

THE MEASUREMENT OF  $^{47}$ Ca CALCIUM ABSORPTION IN  
HEALTH AND DISEASE

by

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Material published before submission of this Thesis (see Appendix A).

MACLEOD, M.A. (1971). Measurement of oral calcium absorption from the gut by external isotope counting. Journal of the Royal Naval Medical Service. 57. 88-91.

MACLEOD, M.A., and BLACKLOCK, N.J. (1974). The application of an external isotope counting technique in the measurement of calcium absorption in urolithiasis. Proceedings of the International Symposium on Radionuclides in Nephrology. Berlin.

MACLEOD, M.A., and BLACKLOCK, N.J. (1974). <sup>47</sup>Calcium absorption in Urolithiases. British Journal of Urology, 46, 377-384.

MACLEOD, M.A., and BLACKLOCK, N.J. (1974). The effect of cellulose phosphate on intestinal absorption and urinary excretion of calcium. British Journal of Urology. 46, 385-392.

## SUMMARY

This work is concerned with the measurement of calcium absorption from the gut in healthy controls and in patients with diseases known to be affected by, or to have an affect on, calcium absorption.

Among the factors which regulate normal gastro-intestinal calcium absorption, current thought recognises calcium intake, vitamin D and parathyroid hormone as playing an important part. It is well documented that calcium absorption is reduced in states of malabsorption, hypoparathyroidism and in patients with chronic renal failure, and raised in hyperparathyroidism, urolithiasis and idiopathic hypercalciuria.

Difficulties inherent in classic calcium balance techniques have prompted a search for more practical and reliable methods of measuring the degree of impairment of calcium absorption. Chapter I describes the use of a chamber scintillation counter to precisely determine the fractional absorption of radioactive  $^{47}\text{Ca}$  from the gut involving only a few minutes of the patients time and obviating the need for hospitalisation in a metabolic ward. The effects of diet, calcium carrier load, age and skin pigmentation on calcium absorption is discussed.

The application of this method to measuring calcium absorption in patients with urolithiasis is detailed in Chapter 2. Of the group of renal stone formers studied 82% were found to be hyperabsorbers of calcium. Recurrent stone formers showed a significantly greater hyperabsorption of calcium than single stone formers and there was better correlation in the recurrent cases with simultaneous calcium excretion.

The role of sodium cellulose phosphate in the management of cases of recurrent urolithiasis who exhibit calcium hyperabsorption is



discussed in Chapter 3 and some of the factors affecting the efficacy of this preparation are investigated.

It is shown that sodium cellulose phosphate can significantly reduce the absorption of calcium from the intestine with concomitant diminution of urinary calcium excretion. The plasma levels of other divalent cations do not appear to be influenced.

Subsequent investigation in some of the patients exhibiting calcium hyperabsorption, high urinary calcium and hypercalcaemia showed them to have primary hyperparathyroidism. Measurements of calcium absorption and other significant parameters in these patients before and after sub-total parathyroidectomy are detailed in Chapter 4.

From these investigations it is evident that the main factor in producing hypercalciuria and the renal stones in patients with normal serum calcium, phosphorus and parathormone is a primary abnormality in intestinal absorption resulting in calcium hyperabsorption. These patients are readily differentiated from patients with 'resorptive' hypercalciuria and renal stones due to hyperparathyroidism.

CONTENTSPage

ACKNOWLEDGEMENTS	1
PREVIOUSLY PUBLISHED MATERIAL	2
SUMMARY	3
CONTENTS	5
GENERAL INTRODUCTION	7
CHAPTER 1    The application of an external isotope counting technique in the measurement of calcium absorption	11
1.1    Introduction	11
1.2    Materials and Methods	12
1.3    Results	23
1.4    The effect of diet and calcium carrier load on calcium absorption	27
1.5    The effect of age and skin pigmentation on calcium absorption	28
1.6    Discussion	32
CHAPTER 2    The measurement of calcium absorption in urolithiasis	37
2.1    Introduction	37
2.2    Materials and Methods	39
2.3    Results	40
2.4    Discussion	45

CHAPTER 3	The role of cellulose phosphate in the treatment of urolithiasis	52
3.1	Introduction	52
3.2	Materials and Methods	53
3.3	Results	54
3.4	Discussion	65
CHAPTER 4	Calcium absorption in hyperparathyroidism	69
4.1	Introduction	69
4.2	Materials and Methods	71
4.3	Results	72
4.4	Discussion	75
REFERENCES		82
APPENDIX A	Published Papers	90

## GENERAL INTRODUCTION

During the past decade, interest in calcium metabolism has greatly expanded and with current methods of measuring calcium absorption both time consuming and requiring hospitalisation with strict metabolic regimen, a simple more direct method would be of great advantage. Measurement of serum calcium alone will only give the equilibrium figure between calcium input into the bloodstream (net absorption and bone resorption) and calcium output (bone mineralisation, renal excretion and intestinal secretion) at the time of measurement and will not necessarily reflect quite large changes in any one of these parameters. For example, the concept that there exists a 'steady state' or physio-chemical equilibrium between blood and bone calcium, the level of which is determined by parathyroid activity, is not supported by recent work (Nordin and Peacock, 1969).

Abnormalities of gastro-intestinal absorption of calcium are well recognised features in many disorders of calcium metabolism thus accurate in vivo measurement of absorption will of necessity lead to a greater understanding of the cause and effect of these abnormalities than in vitro measurements of serum and urinary calcium alone.

The mechanism for the increased urinary excretion of calcium in patients with hypercalciuria has not yet been established. Henneman et al (1958) believe that the possible sequence of events, leading to idiopathic hypercalciuria was 'Pyelonephritis, tubular damage, decreased reabsorption of calcium, hypercalciuria, tendency to hypocalcaemia, compensatory parathyroid hyperplasia, hyperphosphaturia and finally hypophosphataemia'. They suggested that if such a sequence of events could be proven the syndrome could be termed 'primary renal tubular hypercalciuria'. This view, that the primary defect was one of tubular

handling of calcium, has been supported by other workers in independent studies (Jackson and Doncaster, 1959; Edwards and Hodgkinson, 1965). More recent work however by Peacock and Nordin (1968) has shown that tubular reabsorption of calcium in patients with hypercalciuria was the same as that in subjects with normal urinary calcium. They found that 'tubular reabsorption of calcium' in hypercalciurics was similar to that in patients with nephrolithiasis and in normal subjects, they concluded that the increased urinary excretion of calcium in most cases of 'idiopathic hypercalciuria' must be due to an increased filtered load of calcium.

Wills et al. 1970 suggest that "Calcium is excreted by the kidneys through a combination of filtration and tubular reabsorption of the diffusible fraction of the serum calcium. Normally 95-99% of the filtered calcium is reabsorbed. Thus a 5% increase in the glomerular filtration rate, without change in tubular reabsorption, could cause a four-to-five fold increase in calcium excretion; similarly a 5% change in reabsorption could cause a six-fold change in urinary excretion (Kleeman et al). Thus a very small change in the diffusible serum calcium fraction following gastro-intestinal absorption could, by increasing the filtered load account for hypercalciuria". This is surely too facile an explanation as it is only true if the tubular reabsorption remains constant in absolute terms rather than as a percentage.

In the 125 cases of urolithiasis studied in this work 82% were found to be hyperabsorbers of calcium. Recurrent stone formers showed a significantly greater hyperabsorption of calcium than single stone formers. There was also better correlation in the recurrent cases between hyperabsorption and hypercalciuria.

The link between hyperabsorption of calcium and hypercalciuria in the formation of renal stone lies, to my mind, in the increase in the filtered load of calcium in the nephron following hyperabsorption of calcium due to an inherent metabolic abnormality. Calcium in excess is known to be a cell toxin and, as detailed in Chapter 2, stone formation may be subsequent to an extruded calcified tubular cell acting as a nidus for crystallisation. The 'inherent metabolic abnormality' giving rise to intestinal hyperabsorption of calcium has at the moment not been determined but I strongly suspect that it is partly involved with the metabolism of refined carbohydrates in modern diet and preliminary investigations by us in this area are encouraging.

There are now a number of ways by which urinary calcium can be reduced. High fluid intake may be recommended for all stone formers as a basic protective measure. A low calcium diet of less than 50 mg daily should provide an effective reduction in urinary calcium (Nordin, 1972) but due to the presence of calcium in so many kinds of food and in drinking water, such a diet is hardly possible. It is unpalatable, lacks many essential trace elements and requires a considerable amount of will-power on the part of the patient to maintain it consistently. In such a situation, cellulose phosphate, an ion exchange cellulose with a particular affinity for calcium has certain advantages. In the stomach it exchanges sodium for calcium which is bound to the cellulose and eliminated in the faeces thus preventing the absorption of dietary calcium. Part of this work shows the effect of cellulose phosphate on intestinal calcium absorption and the short and long term effect on certain other essential divalent cations.

Although the importance of vitamin D in the regulation of gastrointestinal calcium absorption is universally recognised (Nicolayson,



Eeg-Larsen and Malm, 1953), the exact role for parathyroid hormone in the absorption of calcium from the gastro-intestinal tract had been largely assumed from indirect evidence derived from clinical states associated with abnormal parathyroid activity. Wills et al. (1970) attempted to define such a role and showed in normal subjects, and one patient with idiopathic hypoparathyroidism, treated with parathyroid extract that "In all subjects there was a small increase in the gastro-intestinal absorption of calcium during the administration of parathyroid extract". From this they deduced that parathyroid hormone plays a "small and significant role in enhancing the gastro-intestinal absorption of calcium in man". Previous studies (Albright et al. 1929; Aub et al. 1937) had failed to detect this effect because faecal calcium excretion was used to determine calcium absorption in the classical way. It is probable that faecal calcium excretion does not give a true estimate of intestinal calcium absorption in a situation where the serum calcium concentration is changing, as it does with administration of parathyroid extract. In such a situation the increase in serum calcium concentration could induce an increase in endogenous faecal calcium. If the extra calcium is secreted into the intestinal tract at a point lower than the absorption site, any changes in absorption would be masked.

The use of an external scintillation counting technique to measure calcium absorption, as detailed in this work, has overcome this problem for it provides a direct measurement of the total absorbed calcium load. Measurements detailed in Chapter 4 support the views of Wills et al, discussed above, on the significance of parathormone in calcium absorption, and provide a method for differentiating between the 'absorptive' hypercalciuria of nephrolithiasis and the 'resorptive' hypercalciuria of hyperparathyroidism.

## CHAPTER 1

### THE APPLICATION OF AN EXTERNAL ISOTOPE COUNTING TECHNIQUE IN THE MEASUREMENT OF CALCIUM ABSORPTION

#### 1.1 Introduction

Radionuclides of calcium have been used in an attempt to measure the absorption of calcium from the gastro-intestinal tract since Garner (1960) and his associates measured the fractional excretion in urine of  $^{45}\text{Ca}$  after administering two doses of radioactive calcium, one given intravenously and the other by mouth. The absorbed fraction of the  $^{45}\text{Ca}$  was then calculated by assuming that the fractional excretion of the absorbed part of the oral dose is identical to that of the entire intravenous dose. This method was later developed by Degrazie et al. (1965), Bronner (1962) and Dellipiani, Tothill and Girdwood (1964), using either the same technique or modifying it by giving two radionuclides,  $^{45}\text{Ca}$  and  $^{47}\text{Ca}$ , at the same time.

Although these workers based their calculation on measurements of the amount of activity excreted in the urine, an equally valid calculation can be based on measurements made of activity present in blood or in any other body calcium pool, so long as the assumption of identical distribution of the intravenous dose and the absorbed part of the oral dose holds.

In 1964 Lutwak and Shapiro described a technique for measuring calcium absorption in man using a large volume liquid scintillation counter to count forearm radioactivity after an oral dose of  $^{47}\text{Ca}$ . This technique, however, uses only a single oral dose and because factors other than absorption influence arm radioactivity their calculations are based on assumptions that are uncertain.



With the advent of large volume chamber scintillation counters a much more accurate and exact technique, again based on the assumption that the distribution in the body of an absorbed part of an oral dose is identical to that of an entire intravenous dose, has become available (Curtis, Fellows and Rich, 1967, Wills et al. 1970, Macleod, 1971). The method described in this work measures the fraction of a known intravenous dose of  $^{47}\text{Ca}$  in the forearm and assumes that this will be the same as that of the absorbed part of an oral dose. Knowing the exact amount of the radionuclide given orally it is then easy to calculate the exact amount absorbed from the gut.

In an effort to check the validity of this method it was compared with an independent measure of uptake of the oral dose by stool counting.

## 1.2 Materials and Method

Twenty male control subjects were selected who had no evident disorder of calcium metabolism or intestinal function and who were all on a normal diet at the time of investigation. The radionuclide used was  $^{47}\text{Ca}$ , a 1.31 MeV gamma emitter with a 4.53 day half life. The forearm being relatively small and freely mobile is especially suited to external counting and was used in all measurements. In all subjects preliminary serum calcium and 24-hour urinary calcium measurements were made. (Table 1.1).

The apparatus used to carry out arm activity measurements comprised a large volume lead chamber, constructed to my design by J & P Engineering, Reading, incorporating two separate NaI (Tl) 4-inch scintillation crystals in opposition with a rubber coated arm rest and hand grip between them to ensure constant geometry when counting the forearm on

subsequent days. (See Plates I, II and III).

Counts were recorded on an Ortec timer/scaler, incorporated in a standard NIMS modules bin, the output being measured by covering the 1.3 MeV photopeak of  $^{47}\text{Ca}$  in order to reject the low energy contribution of  $^{47}\text{Sc}$ . Standards were used to check the calibration of the counter at each measurement.

Preliminary studies with four of the subjects established that it took approximately 20-hours for the effective decay of 1  $\mu\text{Ci}$  intravenous dose of  $^{47}\text{CaCl}_2$  to become exponential in the tissues, bone and blood.

This was achieved by serial counting of the forearm at one-hourly intervals and plotting the subsequent curves. All the curves obtained differed little in appearance and were essentially biphasic. The first 8-hours showed a step appearance and exhibited a 'plateau' effect from 2-6 hours followed by a reduction in activity which became exponential at about 20-hours.

In all subjects measured in this way the 24-hour point lay on the exponential part of the decay curve and was thus selected as a suitable time at which to measure arm activity. The compound curve for these four subjects is shown in Figure 1.1 without correction for physical decay.

In order to ascertain the time taken by the absorbed fraction of an oral dose to reach a similar equilibrium in the forearm, four further subjects were each given an oral dose of 10  $\mu\text{Ci}$   $^{47}\text{CaCl}_2$  in 100 mg calcium gluconate carrier solution made up to 100 ml with water to drink on a fasting stomach. Serial arm counts were obtained in a similar manner to that used for the measurement of the intravenous dose.

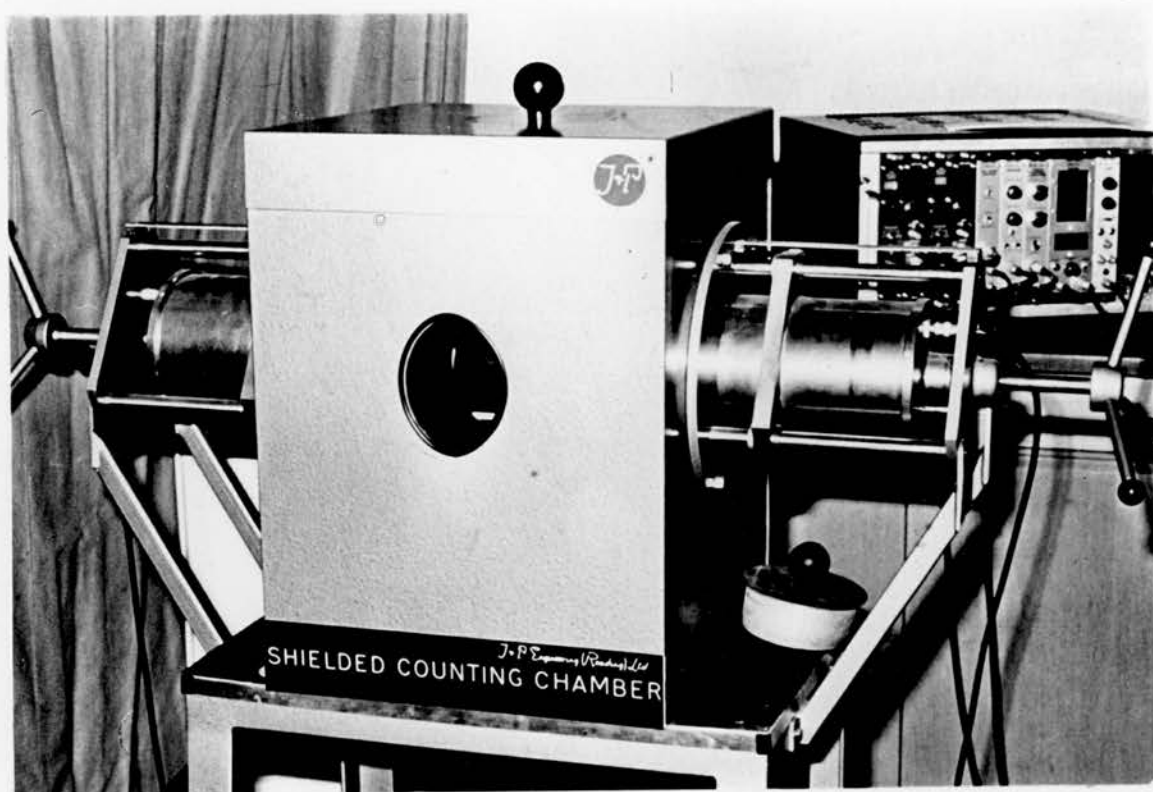


Plate 1.1. Large volume chamber scintillation counter used for forearm counting.

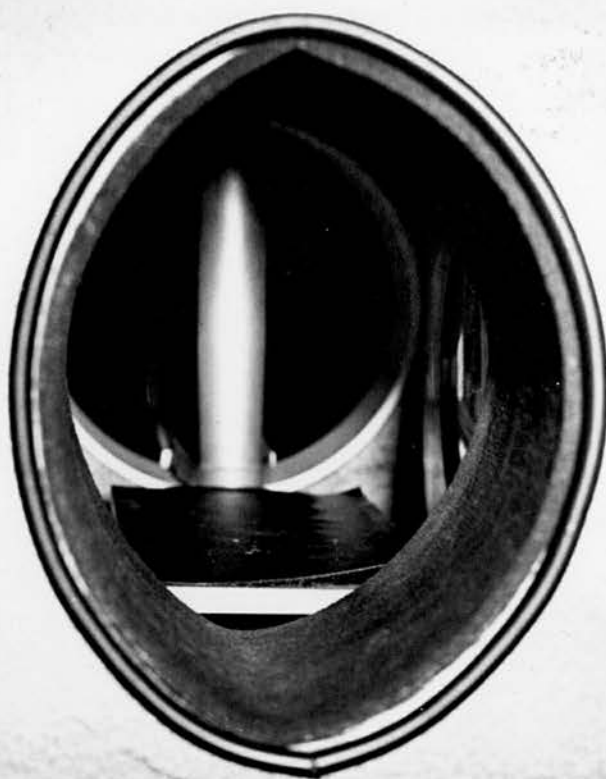


Plate 1.2. Shielded crystals and arm rest from the front port used for inserting the arm.

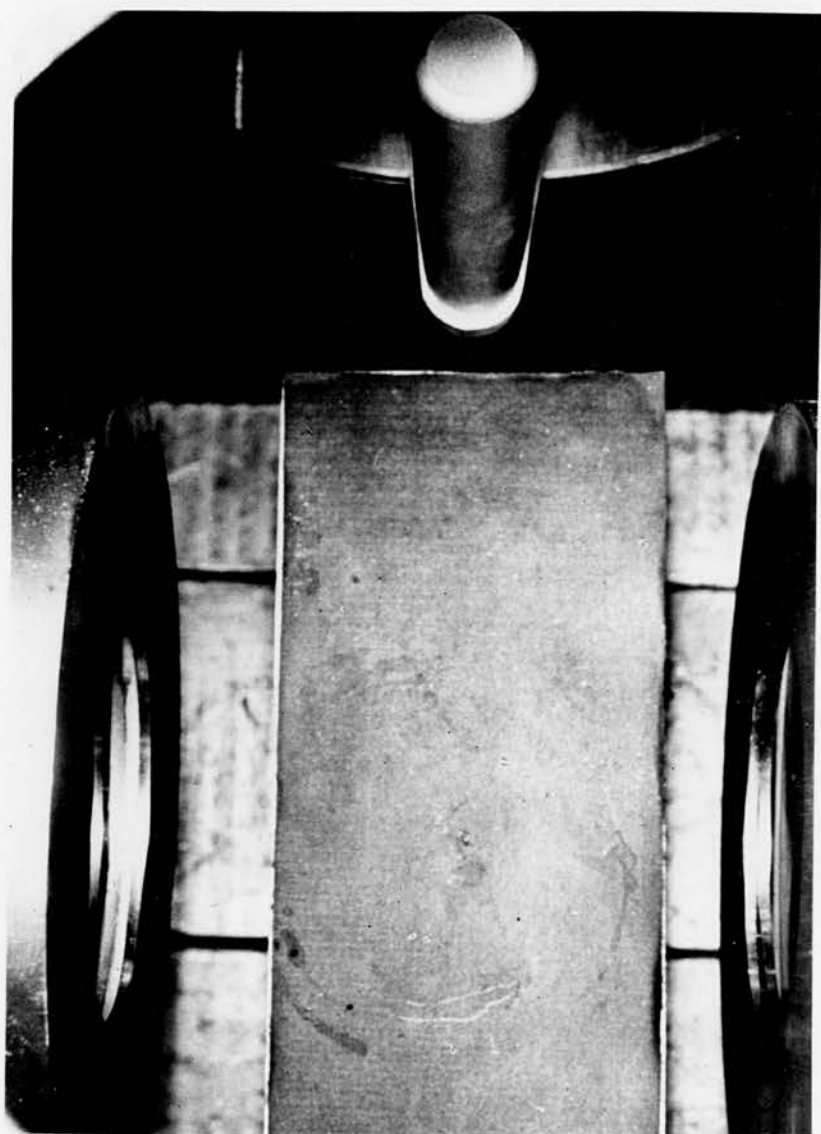
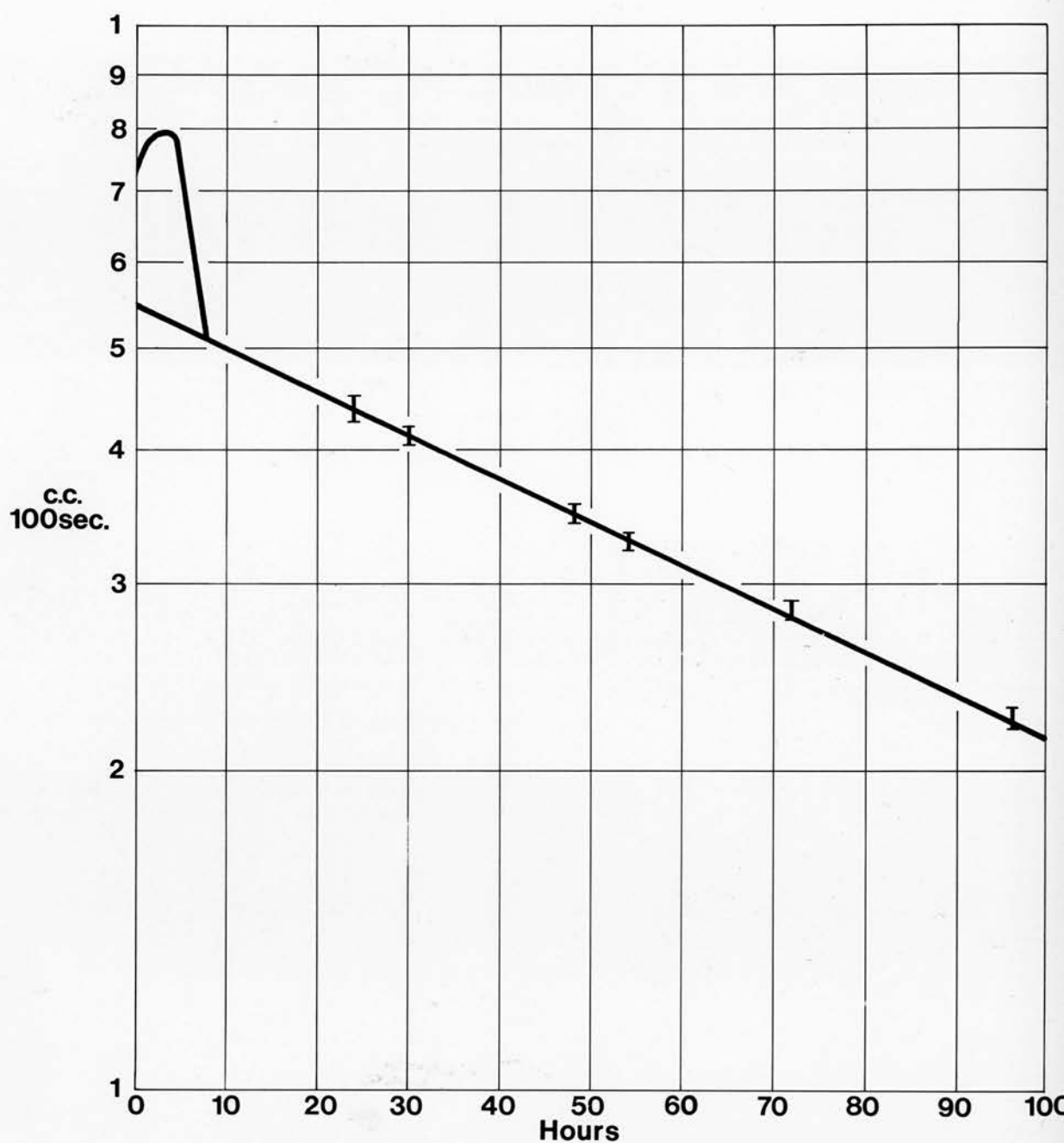


Plate 1.3. Crystals and arm rest from the normally closed port in the top of the chamber used for introducing bulk species for counting.



**FIG 1.1** Mean  $^{47}\text{Ca}$  effective decay  $\pm$  S.D. in the forearm following I.V. injection of  $1\ \mu\text{Ci}$   $^{47}\text{CaCl}_2$  in four control subjects.

The resultant curves obtained showed that, on average, 20-hours were required for the curve to become exponential in the tissues of the forearm following absorption of the absorbed part of the oral dose from the intestine in the fasting state. (See Figure 1.2). Absorption of the absorbed fraction of the oral dose is complete by 2 hours in a fasting stomach. (Degrazie et al. 1965; Avioli et al. 1965) and this is supported by the initial part of the curve (Figure 1.2).

Having obtained these two necessary parameters all the subjects had their calcium absorption measured in the following manner.

On Day 1, each subject was given about  $1 \mu\text{Ci } ^{47}\text{CaCl}_2$  in 1 ml. saline intravenously, the exact volume administered being determined by weighing. On Day 2, 24-hours after the injection, the background count rate was measured with the subject in position beside the chamber but with his arm outside. (Plate 4).

Following this, the forearm was inserted into the chamber and counted for 100 seconds (Plate 5).

On completion each subject was given to drink about  $10 \mu\text{Ci } ^{47}\text{CaCl}_2$  in 100 mg calcium gluconate solution made up to 100 mls with water. Subjects fasted at least 12 hours before and 2 hours after this dose. On Day 3, background count rate and arm count rate were measured again, on this occasion 26 hours after the oral dose on Day 2, the additional 2 hours being the time taken for full absorption of the absorbed part of the oral dose (see Figure 1.2).

A similar final measurement was made on Day 4, 52 hours after the oral dose in order to establish a biological decay factor.



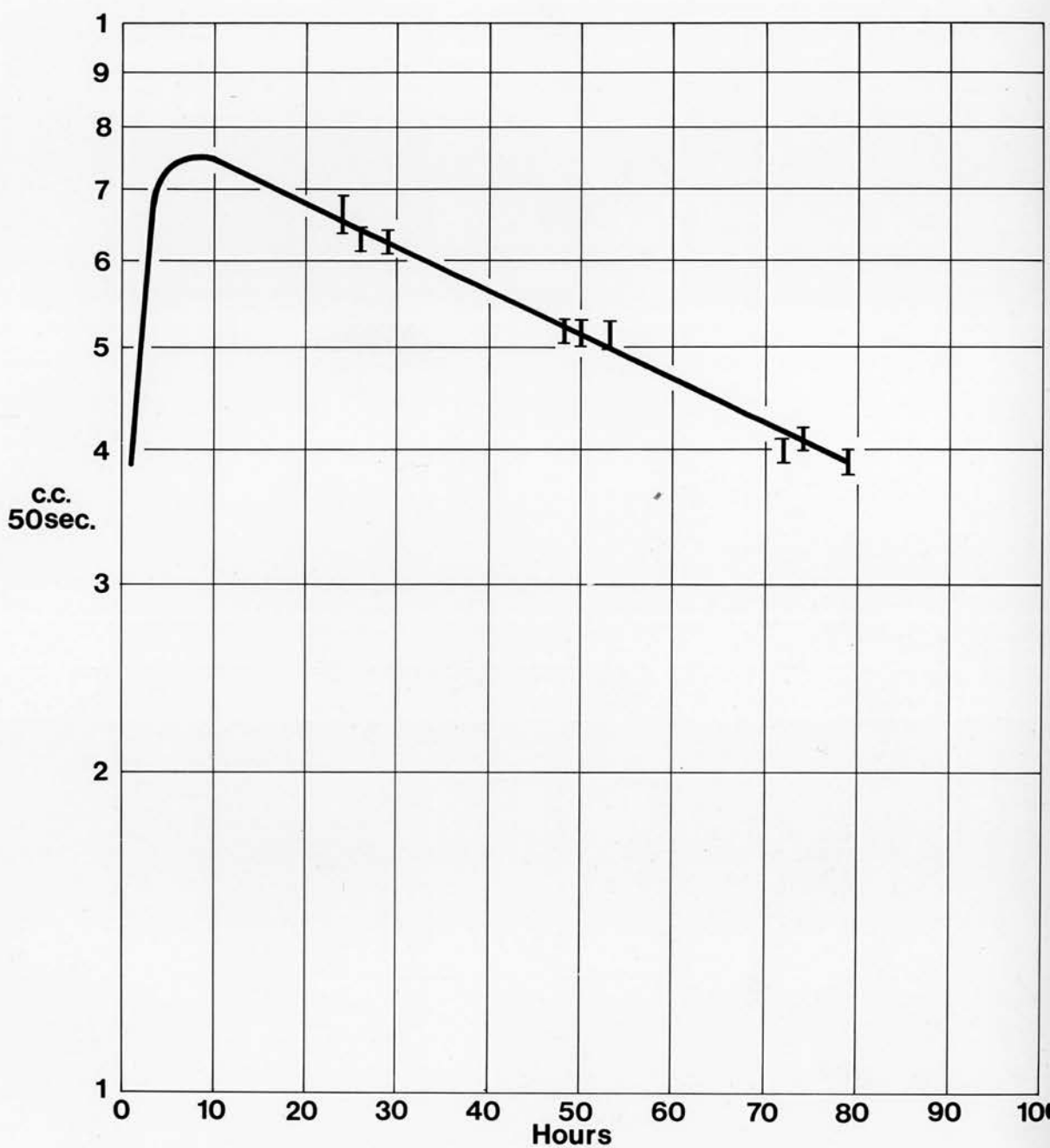


Plate 1.4. Subject in position for background counting.





Plate 1.5. Subject in position for counting with arm introduced into chamber.



**FIG 1.2** Mean effective  $^{47}\text{Ca}$ . decay in the forearm following  $10\ \mu\text{ci}\ ^{47}\text{CaCl}_2$  oral dose in four subjects.

### Calculations

Arm count rate corrected for body background and decay was expressed as arm activity (C) measured at 24 hours after injection ( $C_1$ ), 26 hours after the oral dose ( $C_2$ ) and 52 hours after the oral dose ( $C_3$ ). Thus at 24 hours the fractional arm accumulation ( $C_1$ ) of the intravenous dose (I.V) was  $\frac{(C_1)}{(I.V)}$

At 50 hours the fractional arm accumulation ( $C_2$ ) of the absorbed fraction (F) of the oral dose (O) was  $\frac{(C_1)}{(I.V)} \times (F) \times (O)$  plus the residual activity from the intravenous dose expressed as  $(C_1) \cdot (B)$  where (B) equals the biological decay factor for the 26 hour period since the measurement of ( $C_1$ ).

$$\text{ie. } (C_2) = \frac{C_1}{I.V.} \times F \times O + C_1 \times B$$

Thus the absorbed fraction of the oral dose is:

$$(F) = \frac{(C_2 - C_1 \times B \times I.V.)}{C_1 \times O}$$

The biological decay factor (B) was determined by measuring arm activity at the end of a further 26 hours ( $C_3$ ) and, assuming (B) is not time dependent, then  $B = \frac{C_3}{C_2}$ .

Substituting and simplifying gives the expression:

$$F = \left\{ \frac{C_2}{C_1} - \frac{C_3}{C_2} \right\} \times \frac{IV}{O}$$

In order to check the validity of the method and to ascertain to some degree, the accuracy of the measurements made of fractional calcium absorption, four of the control subjects had concomitant conventional stool counts carried out as an independent measure of body incorporation of  $^{47}\text{Ca}$ .

On the night before the oral dose of  $^{47}\text{CaCl}_2$  a standard dose of

carmine marker was given and stool collections were started on the appearance of the carmine and continued until all the carmine had passed (this took about 4-5 days).

The stools were collected as a single pooled specimen for each subject and liquidised. These were then counted in the large volume chamber used for arm counting, a special aperture in the top of the chamber being included by the manufacturers J. & P. Engineering, Reading, especially for the counting of 24 hour urine and faecal samples (Plate 6). The results were then compared with standards of similar volume and consistency.

The fraction of the oral dose incorporated in the body (A) was calculated from:

$$A = 1 - (\text{fraction of oral dose of } ^{47}\text{Ca recovered in stool})$$

and the results compared with those obtained by arm counting.

### 1.3 Results

The results obtained from these control subjects gave parameters of  $^{47}\text{Ca}$  absorption from the intestine which ranged between 25 and 36 per cent of the oral dose with a mean of 30 per cent. In all of the subjects measurements of serum calcium and 24 hour urinary calcium were within normal limits (Table 1.1).

The comparison between the percentage calcium absorption obtained by arm counting and the absorption calculated from stool recovery in the four subjects studied is shown in Table 1.2.

The mean absorption obtained by stool counting, although not significantly different from that obtained by arm counting is slightly less as would be expected due to re-excretion of part of the absorbed fraction by the lower colon.

TABLE 1.1  
 $^{47}\text{Ca}$  absorption in control cases

Subject	% Calcium Absorption			Serum calcium mg/100ml	24-hr urinary calcium mg
	March 1970	January 1971	July 1972		
R.M.	32%			10.32	245
I.L.	30%	29%	36%	9.84	195
H.G.	28%			10.20	188
D.M.	30%			9.95	220
R.L.	26%	30%		10.15	240
P.C.	28%			9.75	180
R.C.		26%		10.35	200
D.S.	29%		36%	10.43	220
P.B.	25%	27%	26%	9.90	194
P.G.	31%		29%	10.10	185
B.G.		35%		9.84	210
D.J.			36%	9.95	180
S.D.			36%	10.23	180
H.P.			36%	9.84	195
N.S.			35%	9.78	200
P.L.			35%	10.14	215
J.S.			26%	10.23	194
A.K.			25%	9.85	175
G.T.			27%	9.76	185
P.C.			33%	10.20	210

TABLE 1.2  
 Comparison between  $^{47}\text{Ca}$  absorption as  
 measured by arm counting and stool recovery

Subject	% Calcium Abs. (arm counting)	% Calcium Abs. (stool recovery)
I.L.	30	28
H.G.	28	27
D.S.	29	28
P.B.	25	25
Mean	28	27



Plate 1.6. Counting of 24 hour urine and faecal samples.



In order to check the variation, if any, of  $^{47}\text{Ca}$  absorption with time, measurements were repeated over a period of two years in those subjects who were available.

These remained remarkably consistent as can be seen from Table 1.1.

The mean age of these control subjects was 32 years and is comparable with the mean age of the single stone formers (31 years) and recurrent stone formers (34 years) studied in Chapter 2.

#### 1.4 The effect of diet and calcium carrier load on absorption

All the control subjects were on a normal diet at the time of investigation and it was stipulated that they had to be fasting 12 hours before and 2 hours after the oral dose because the two main factors which would obviously affect the absorption of calcium from the gut were:

- a. Pre-existing diet
- b. Carrier load of stable calcium
- a. Pre-existing diet

It has been shown by Holm (1958) that calcium absorption is affected by the pre-existing diet in that patients on long-term balance studies showed an increase in calcium absorption as an adaptation to a low calcium intake. Similarly it has been reported for rats that the small intestine responds to a low calcium diet by increasing the active transport of calcium (Kimberg, Schachter and Schenken, 1961).

From this it is obvious that to achieve accuracy in measuring and postulating a normal range of calcium absorption the pre-existing dietary pattern of both controls and patients must be



known and appropriate corrections made for those on a long-term low calcium diet.

b. Carrier load of stable calcium

In six of the control subjects the effect of varying the amount of the calcium gluconate carrier was studied.

Carrier loads of calcium gluconate varying from 10 mg to 1000 mg were given with the oral dose of  $^{47}\text{CaCl}_2$  and the percentage calcium absorption measured by forearm counting. The results detailed in Table 1.3 show that the percentage calcium absorption, as estimated by this technique, varied inversely with the stable calcium carrier load. (Figure 1.3).

In non-fasting subjects it can be readily seen that the presence of exchangeable  $\text{Ca}^{++}$  ions in food in the intestines at the time of the oral dose would affect the amount of physical carrier available and in addition other substances such as phytic acid and phytates would readily bind with free  $^{47}\text{Ca}^{++}$  rendering it insoluble and unabsorbable.

1.5 The effect of age and skin pigmentation on absorption

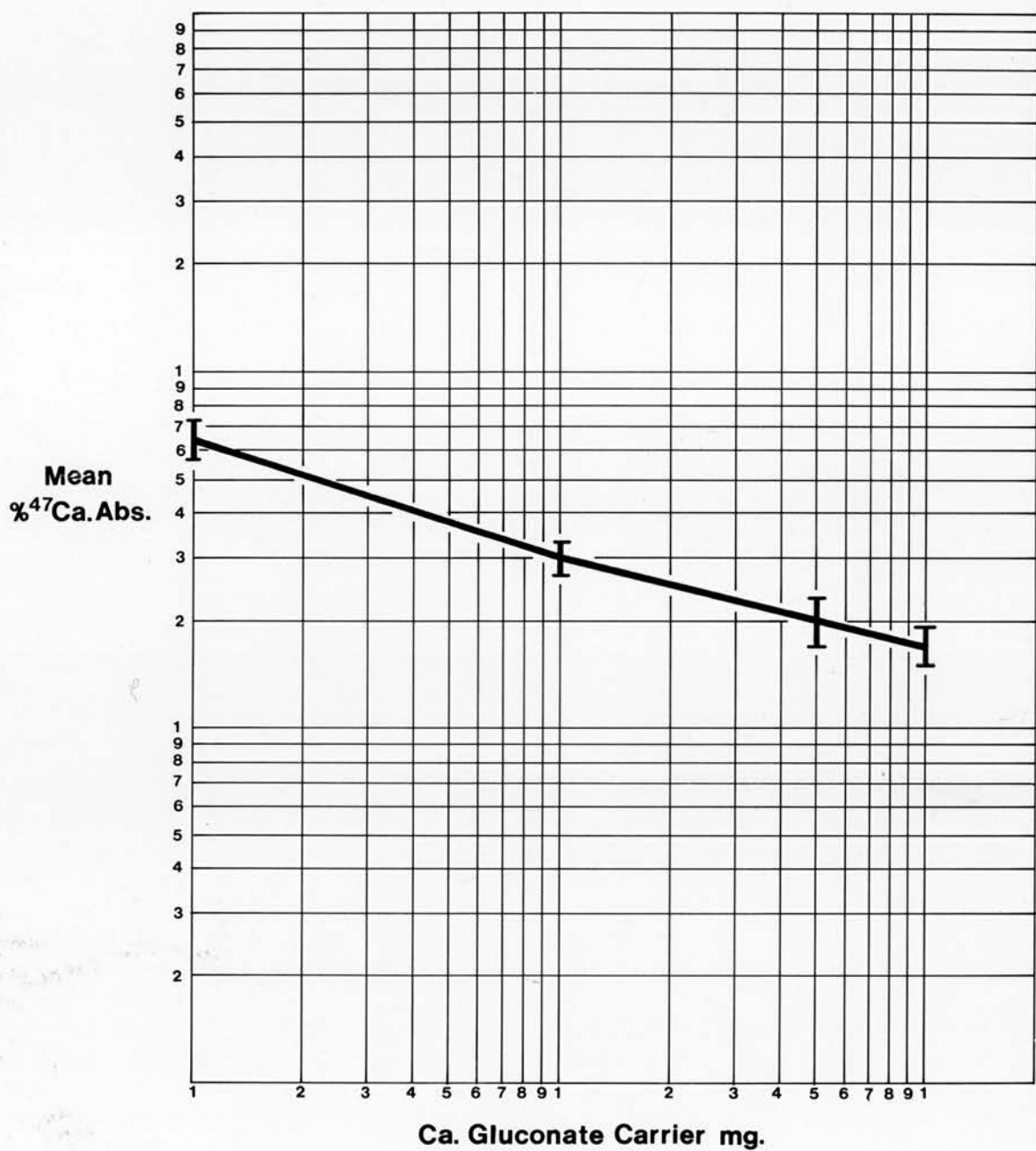
In the few young men we have investigated for urolithiasis we found that their calcium absorption was much higher than was expected. In all of these the epiphyses had not closed. On repeating the measurements with several 'young' controls whose epiphyses, on the evidence of their compulsory annual X-ray, had not closed, they consistently showed a normal range of absorption much higher than that obtained in 'adult' men (see Table 1.4), and thus by definition the control subjects used in Table 1.1 were all over the age of 20 years.

Again we have collected substantial evidence and are at the moment

TABLE 1.3

Percentage calcium absorption for various calcium  
gluconate carrier loads with mean absorption  $\pm$  SD

Subject	% Calcium Abs. with differing calcium carrier loads			
	10 mg	100 mg	500 mg	1000 mg
I.L.	70	30	24 .	20
P.G.	65	31	19	16
B.G.	75	35	18	19
D.M.	58	30	25	17
R.L.	55	26	20	15
R.C.	66	26	17	15
Mean Abs.	65 $\pm$ 8	30 $\pm$ 3	20 $\pm$ 3	17 $\pm$ 2



**FIG 1.3** Mean percentage calcium absorption  $\pm$  S.D. compared with calcium gluconate carrier load in mg.

TABLE 1.4

Percentage calcium absorption, serum calcium and 24-hour urinary calcium in patients and controls in whom the epiphyses had not closed at the time of measurement

Subject	Age	Diagnosis	Serum Calcium mg/100ml	% Calcium Abs.	24-hr Ca excretion mg
K.W.	17	Ureteric Colic	10.35	53	250
D.J.Y.	17	Ureteric Colic	9.28	50	198
P.S.	16	Renal Colic	10.20	54	220
C.M.J.	19	Renal Colic	10.32	54	245
B.M.	18	Control	9.92	52	170
D.P.	17	Control	10.34	32	180
F.A.	18	Control	10.32	44	212
P.S.	19	Control	9.84	44	200
C.D.	18	Control	9.56	44	180
W.P.N.	19	Control	10.45	45	240
M.N.S.	18	Control	10.35	53	210
W.D.J.	18	Control	10.42	54	215
S.K.	18	Control	9.73	28	175

conducting an investigation into the effect of skin pigmentation on calcium absorption. Since we began to use this technique we have seen 8 negro and Indian patients referred for uro-genital investigations. It was noted that their calcium absorptions were usually in or below the 'normal' range and subsequent measurements on 'black' controls verified this. The preliminary results are presented in Tables 1.5 and 1.6.

#### 1.6 Discussion

The principle advantage which recommends this external counting method of measuring calcium absorption is its simplicity. Uncertainty regarding complete stool and urine collection and accuracy of the meticulous laboratory techniques is avoided and the patient is not embarrassed or inconvenienced. It also avoids the inaccuracy introduced in the stool collection method by the excretion of previously absorbed calcium by the lower colon. Sources of error inherent in the technique lie in the prior assumptions and the experimental conditions obtained.

Several theoretical factors should be considered in interpreting the results of this method. After oral administration of  $^{47}\text{CaCl}_2$  the rate of uptake of isotope into the forearm is a complex function of continually changing input into blood with varying rates of uptake by the forearm thus differing from the intravenous dose after which the forearm activity reflects uptake from a single instantaneous input. The ratio of forearm activities, oral to intravenous, therefore does not give a precise estimate of calcium absorption. Nevertheless the results show that this ratio of forearm activities does in fact reflect mainly the gastro-intestinal absorption of calcium.

It is assumed that the oral dose is promptly absorbed 2 hours

TABLE 1.5

Percentage calcium absorption, serum calcium and  
24-hour urinary calcium in black skinned controls

Subject	Age	Serum Calcium mg/100 ml	24-hr Urinary Calcium mg	% Calcium Absorption
C.C.	19*	10.24	195	29
S.B.S.	22	9.82	205	29
S.S.H.	18*	10.00	210	31
P.R.R.	29	9.72	185	20
R.B.	20	9.85	195	17
H.H.	21	10.20	208	23

\* Epiphyses not closed

TABLE 1.6

Percentage calcium absorption, serum calcium and 24-hour urinary calcium in black-skinned patients with urolithiasis

Subject	Age	Serum Calcium mg/100 ml	24-hr Urinary Calcium mg	% Calcium Absorption
N.J.	23	10.23	240	45
C.L.	41	9.74	215	24
D.J.	42	10.15	230	28
A.J.	27	9.85	198	27
C.A.	23	9.75	210	35
F.A.	33	10.10	195	28
P.A.	26	9.80	200	29
P.L.F.	30	9.35	220	23



after administration and reaches equilibrium in the tissues of the forearm by 18-20 hours. This is largely demonstrated in Figure 1.2, and there is ample evidence by other workers that in a fasting subject, under the conditions of the test, absorption is rapid and essentially complete in 2 hours (Degrazie et al. 1965; Avioli et al. 1965).

Furthermore, the rate of change of arm activity becomes relatively slow 20 hours after administration of radio calcium (see Figure 1.2) and accordingly errors introduced by an incorrect estimation of the time of absorption will be small.

A correction for residual arm activity from the intravenous dose must be made at the time of measuring forearm activity following the oral dose and this is done by estimating the biological decay factor as explained in the calculations.

There is a considerable amount of isotope remaining in the gut at the time of counting 26 and 50 hours after the oral dose, but, with correct positioning of the patient in relation to the counting chamber, ie. to the side and close against the lead wall so that no part of the body is seen through the port by the detectors, and careful background counting the effect of this surplus radioactivity in the gut can be minimised.

Other factors which became increasingly evident after 2 to 3 years experience with the technique is that the normal range of 25-35% absorption of the oral dose does not apply to those in whom the epiphyses have not closed and to those who have heavily pigmented skins.

In young men with actively growing bone the amount of calcium required to lay down new osseous tissue is obviously met by greater calcium absorption than is seen in those in whom growth has stopped.



This is reflected in the higher 'normal' range of absorption seen by us in young men controls. These were measured subsequent to our suspicions being raised by abnormally high calcium absorption seen in two young sailors referred for urological investigation with renal stone.

In the case of those of Negro and Indian descent and a below 'normal' calcium absorption, an interesting theory is that their heavily pigmented skins which provides protection against the large dose of ultra-violet light experienced in the tropics where prolonged sunshine is common, is too effective a barrier for the moderate amount of sunshine found in these isles. This would interfere with the ultra-violet light - calciferol - Vitamin D reaction and we are at present looking at controls exposed to varying doses of ultra-violet light before taking the oral dose of calcium.

The results to date are most encouraging showing increases in calcium absorption of 1.5 to 2 times over normal following 10 minute doses of ultra-violet light.

Obviously then, the questions of ephiphysial closure and skin pigmentation must be considered when using this technique and a better understanding of the factors involved will, I hope, be the outcome of the present study.

THE MEASUREMENT OF CALCIUM ABSORPTION IN UROLITHIASIS

2.1 Introduction

The abundant research already done on urolithiasis has clearly shown that stone formation in any one case is a result of a number of abnormal conditions. These include abnormalities of the calyceal system and pelvi-ureteric out-flow of urine which result in stasis and, more commonly, abnormalities of the urine itself. Infection is now uncommon in Western communities as an initiating factor in urinary tract stone.

Of the urinary abnormalities, the presence of excessive amounts of calcium, or other stone constituents, and the relative lack in the urine of substances which inhibit precipitation of calcium salts have been two of the most promising lines of further research.

An association between hypercalciuria and calcium urolithiasis was described by Flocks in 1939 but subsequent work has fallen short of establishing the relationship between these two phenomena. If hypercalciuria is defined as the excretion of more than 300mg of calcium in 24-hours in the male and more than 250mg of calcium in 24-hours in the female Hodgkinson and Pyrah, (1958) about 8 per cent of the general population are hypercalciuric. In a group of patients forming calcium containing renal stones, Melick and Henneman (1958) found that 32 per cent had hypercalciuria. Similar findings have been made by Hodgkinson and Pyrah (1958), Boyce et al. (1958), Harrison (1959) and Litin et al. (1961). Whilst an excessive urinary calcium is present in other specific diseases, hypercalciuria occurring in the absence of any of these was described by Albright et al. in 1953. This

syndrome was defined as the occurrence of a high urinary calcium in association with normal serum calcium, a tendency to hypophosphatemia and renal stone formation and it has been recognised by others (Henneman et al. 1958; Harrison, 1959; Parfitt et al. 1964 and Edwards and Hodgkinson, 1965). There are several possible causes of this hypercalciuria but Cannigia, Gennari and Cesari (1965) suggested that it was primarily absorptive in origin. Peacock, Hodgkinson and Nordin (1967) showed the importance of dietary calcium in demonstrating hypercalciuria, suggesting that the hypercalciuria in stone formers was probably due to excessive absorption of calcium thus implying that idiopathic stone formers were largely drawn from that segment of the population in whom absorption and therefore urinary excretion of calcium was above average.

The role of enhanced gastro-intestinal absorption in the aetiology of renal stone formation however, has been questioned. Whereas some workers have reported that urinary calcium excretion could be reduced with a low calcium diet (Henneman et al. 1958; Harrison, 1959; Gill and Bartter, 1961; Dent and Watson, 1965; Peacock, Hodgkinson and Nordin, 1967) others have indicated that it did not change (Jackson and Doncaster, 1959; Edwards and Hodgkinson, 1965; Phillips and Cooke, 1967). This apparent discrepancy was probably due to inadequate restriction of dietary calcium in the second group as the case reported by Dent and Watson (1965) did not have a satisfactory reduction in hypercalciuria until distilled water was used for both drinking and cooking. The conclusion reached by these authors was that the primary defect in hypercalciuria could be due to the inability of the intestinal mucosa to limit absorption in the usual way, resulting in excessive calcium absorption. The results reported in this Chapter would tend

to support this view and suggest that a primary defect in the handling of calcium by the intestine plays a crucial part in the increased urinary calcium excretion seen in patients with renal stones and hypercalciuria. This handling defect probably causes small but significant increases in the diffusable serum calcium fraction which results in a significant increase in the filtered calcium load and hence an increased tendency to form calcium containing renal stones.

## 2.2 Materials and Methods

This Chapter is concerned with the study of a group of stone formers and recurrent stone formers in the Royal Navy and the purpose of the investigation was to establish the incidence of hypercalciuria in these two groups and its relationship to intestinal calcium absorption measured by arm counting as detailed in Chapter 1.

All cases of urolithiasis studied were registered in the Renal Stone Survey which is supported by grant from the Medical Research Council and all were either in or out-patients in the Department of Urology of the Royal Naval Hospital, Haslar.

Initially, each patient had a full general and metabolic investigation including excretion urography. The serum calcium, inorganic phosphate, protein and alkaline phosphatase were estimated on at least 4 separate occasions with the patient in the fasting state. Serum calcium was estimated by the method of Keffler and Wolfman, (1964) adapted for autoanalyser, and the upper limit of normal for this laboratory was taken as 10.5mg per 100 ml.

Urinary calcium excretion was measured first of all with the patient on a diet containing calcium supplements since it has been established that hypercalciuria is only detectable at moderately high calcium

intakes (Peacock, Hodgkinson and Nordin, 1967). Thereafter a low calcium diet (150mg calcium per day) was given and, after a period of three days, further measurements of calcium excretion were made to establish the response to this. Urinary calcium was estimated by atomic absorption flame photometry using a Unicam SP.90.

Gastro-intestinal absorption of calcium was measured by the arm counting technique described in Chapter 1.

Since it has been reported that restriction of calcium intake, eg. low calcium diet, will result in an increased absorption of available calcium from the gut (Malm, 1958; Kimberg, Schachter and Schenken, 1961) all the patients prior to January 1972 were on a normal diet except for a fast of 12 hours before receiving the oral dose of  $^{47}\text{CaCl}_2$  on the second day of the test. For various reasons during 1972, 49 of 83 patients so tested had started a low calcium diet of 150mg of calcium daily at the time of the investigation. Of these, the great majority had calcium absorption measured within a day or two of starting the low calcium diet and in no case was the measurement made with the patient more than 5 days on this diet. Comparing the two groups, the results showed no statistical difference; 63 per cent of patients on the low calcium diet and 60 per cent of the patients on a normal diet were absorbing calcium excessively. This suggests that a low calcium diet for a short period of time does not influence the process of absorption from the gut. This observation agrees with that of Wills et al. (1970).

### 2.3 Results

125 cases of urolithiasis were studied and only 2 of this number were female.

Of the 125 patients, 23 (18 per cent) absorbed calcium within the

normal range; 102 (82 per cent) absorbed it excessively. The extent of this hyperabsorption of calcium was variable and is shown graphically in Figure 2.1.

Estimations were repeated in a number of these patients over an 18 month period and these showed that the tendency to absorb calcium excessively remained although there was some variation of the extent of this. (Table 2.1).

A comparison of calcium absorption with 24 hour urinary calcium excretion in the 125 patients showed that all but three who were hypercalciuric were also absorbing calcium excessively from the intestine. (Figure 2.2).

This confirms observations by others (Flocks, 1939; Zisman, Pak and Batter, 1967; Wills et al. 1970).

Two sub groups were formed from the series for comparison. The first was of patients who had formed only a single stone at the time of investigation. The second group comprised those who had formed 2 or more stones in clearly separated instances and were therefore recurrent stone formers. The first group may represent the type of patient in whom stone formation is an isolated incident but it is recognised that with a sufficiently long follow-up period some of these could have recurrences at a later date. In other aspects both groups appeared to be well matched; the mean age of the single stone formers was 31 years and that of the recurrent stone formers 34 years. The difference in mean age was not significant.

Of 78 cases of apparently solitary stone, 59 (76 per cent) showed excessive calcium absorption and 31 (40 per cent) of these were hypercalciuric. Of 47 cases of recurrent stone 42 (89 per cent)



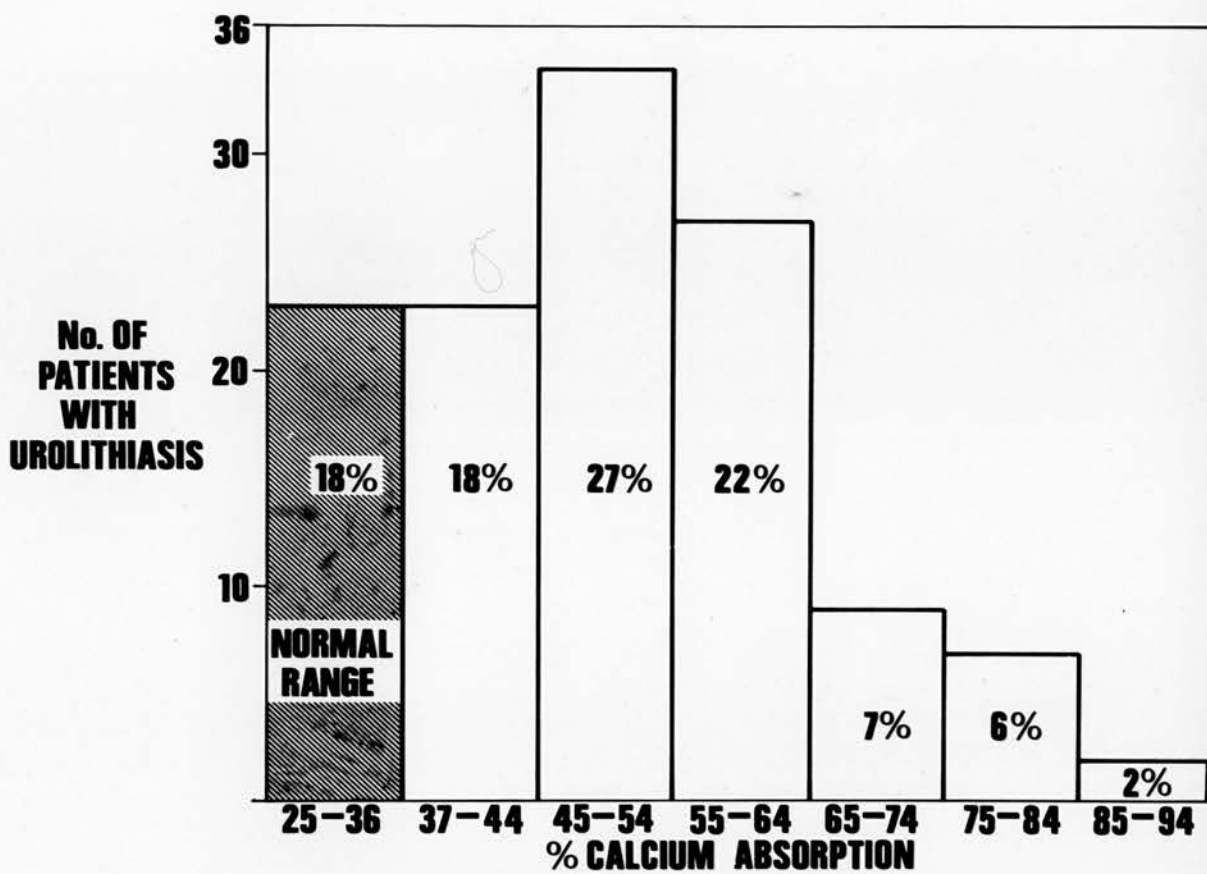


FIGURE 2.1 Variable intestinal hyperabsorption of  $^{47}\text{Ca}$  in 125 cases of urolithiasis.



TABLE 2.1  
Repeat estimations of  $^{47}\text{Ca}$  absorption  
on known hyperabsorbers

Patient	$^{47}\text{Ca}$ Absorption			
T.G.H.	16.11.70	74%	13.9.71	60%
E.J.H.	16.11.70	64%	13.9.71	51%
P.J.D.	14.12.70	76%	19.6.72	52%
B.L.P.	10. 5.71	77%	19.7.71	71%
H.J.T.	7. 9.70	44%	19.7.71	41%
J.F.	20. 9.71	76%	10.7.72	55%

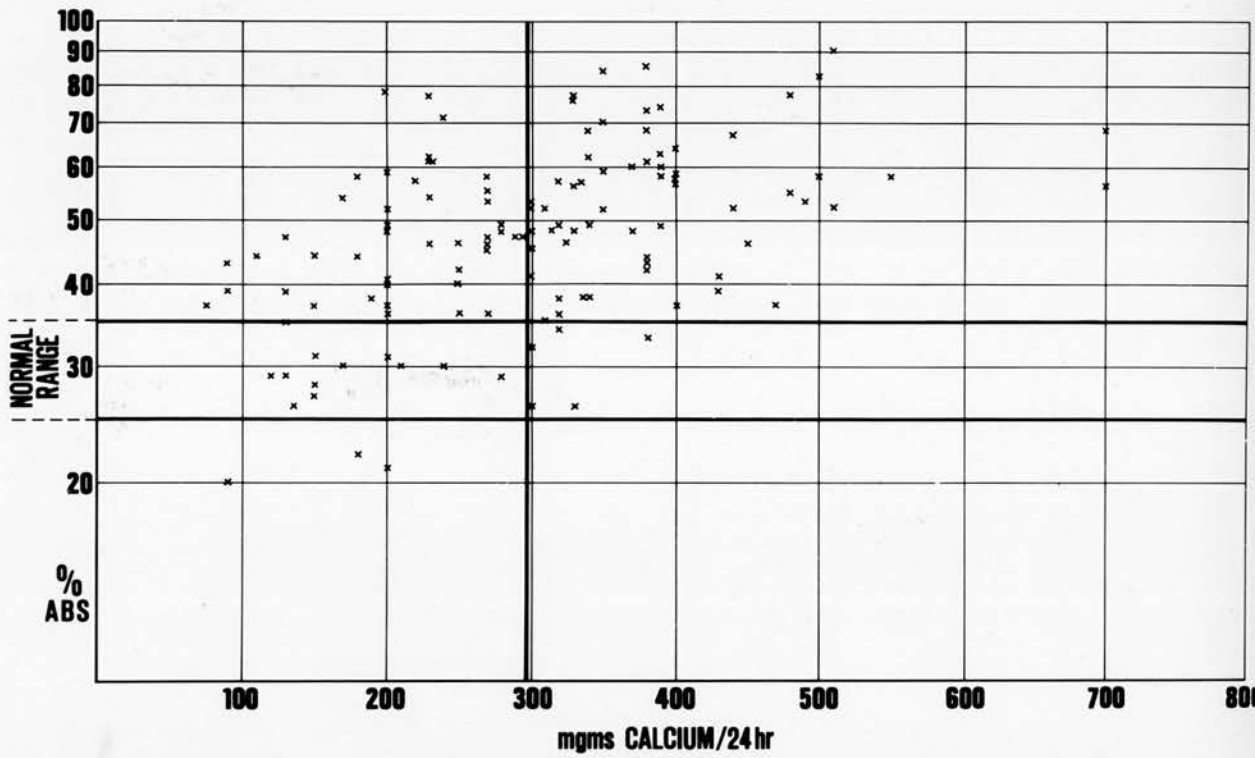


FIGURE 2.2 Comparison of  $^{47}\text{Ca}$  absorption with 24 hour urinary calcium excretion in 125 cases of urolithiasis.

absorbed calcium excessively and of these, 36 (77 per cent) were hypercalciuric (Table 2.2).

In the single stone formers the mean calcium absorption was 46 per cent (SD.13) and the mean 24 hour urinary calcium excretion was 276 mg. (SD.116). In the recurrent group, mean absorption was 56 per cent (SD.16) and mean excretion, 345 mg. (SD.104). The comparison between the two groups shows a significant difference. (Chi - squared test to one degree of freedom  $P < 0.025$ ) even with the probability of "contamination" of the first group by a number of potential recurrent stone formers (Table 2.3).

#### 2.4 Discussion

The incidence of hypercalciuria in all patients referred with renal stone to the Department of Urology in this hospital is approximately 33 per cent. Of the 125 cases of urolithiasis investigated in this study 54 per cent were found to have hypercalciuria but this is likely to be an artificially high figure in that the recurrent stone former will tend to be referred for complete hospital investigation more often than the patient with a single, short-lived incident. Excessive urinary calcium excretion has been ascribed to excessive intestinal calcium absorption (Harrison, 1959; Parfitt et al. 1964; Peacock et al. 1967) and the results from these  $^{47}\text{Ca}$  absorption studies support this concept and confirm that a majority of stone formers, whether they are hypercalciuric or not, absorb calcium excessively from the intestine and this is most obvious in cases of recurrent urolithiasis.

It is apparent from the results that there is only a partial correlation between apparently excessive calcium absorption and the occurrence of hypercalciuria. All but three of the hypercalciurics

TABLE 2.2

Comparative incidence of increased  $^{47}\text{Ca}$  absorption and hypercalciuria in solitary and recurrent stone cases

		$^{47}\text{Ca}$ Absorption	Urinary $\text{Ca}^{++}$ Excretion
		< 36%	< 300 mg/day
Solitary Stone	78	59 (76%)	31 (40%)
Recurrent Stone	47	42 (89%)	36 (77%)

TABLE 2.3

Comparison of mean absorption and urinary calcium excretion in solitary and recurrent stone formers

	Mean $^{47}\text{Ca}$ Absorption	Mean Urinary $\text{Ca}^{++}$ Excretion
Solitary Stone	46% (SD.13)	276 mgm/day (SD.116)
Recurrent Stone	56% (SD.16)	346 mgm/day (SD.104)

$p < 0.025$

were found to absorb calcium excessively but 49 patients who were absorbing calcium in excess from the gut were excreting calcium in normal amounts in the urine at the time of the test. Since the  $^{47}\text{Ca}$  absorption measurement deals only with the percentage absorption of an oral calcium load it is possible that the high absorption figure and normal excretion was due to a low calcium intake prior to the test. All patients, however, were on a standard ward diet at the time with calcium supplement in the form of a pint of milk per day over and above that taken with cereal, tea and coffee. In the circumstances if there was a simple linear relationship between calcium uptake and excretion, greater correlation might have been anticipated. Again urinary calcium excretion is dependent on accuracy of urine collection and it is conceded that in some cases collections might not have been complete. However, since hypercalciuria is assessed on the amount of calcium in a 24 hour collection of urine, diurnal variations of calcium concentration will be concealed and hypercalciuria of varying degree may occur on a number of occasions within a 24 hour period without there being necessary overall hypercalciuria (Marshall and Barry, 1972). It may therefore be inadequate to define hypercalciuria as the excretion of more than 300 mg of calcium in 24 hours in the male and 250 mg in the female (Hodgkinson and Pyrah, 1958). Rose (1967) has pointed out that the normal range of urinary calcium varies from one country to another and may also vary within a country. Watson and Dale (1966) consider that in London the excretion of up to 400 mgms of calcium per day is normal for a man and 300 mgms per day for a woman.

In the series of patients studied here, however, there appears to be closer correlation between intestinal calcium absorption and urinary

calcium excretion in the recurrent than in the apparently solitary stone formers. If dietary differences and possible errors in urine collection are excluded, this suggests that in the latter, calcium is deposited, or stored temporarily after absorption, prior to being excreted at a later date.

An implication of finding an increased absorption of calcium in a high proportion of cases of urolithiasis is that greater quantities of calcium are being presented to the excretory system, and the nephron in particular, for excretion. Calcium is a known potential toxic agent when present in excess within the body and cellular damage due to high local concentrations of calcium might be anticipated in the cells of the nephron or its interstitial tissues. This might be the interpretation of the findings by Anderson (1968) of foci of calcium phosphate precipitation in the kidneys of patients with recurrent metabolic stone. Similar foci were present in patients who had no history of stone formation but they were significantly more prevalent in the stone forming group. The calcium phosphate was present within the interstitial tissues and the epithelial cells of the renal tubules, sometimes extending into the lumen. He found the loop of Henle and the collecting tubules most frequently involved. Boyce (1972), in a study of biopsies of human kidney, has shown accumulations of calcium deposition within the lumen of the nephron and considered that the origins of this material were in the proximal renal tubules and that there was subsequent migration to the collecting ducts. He attributed the high incidence of medullary concretions to the coalescing ductal anatomy. Cook (1972) in a radioisotope study demonstrated a marked calcium concentration gradient ranging from maximal in the papilla tip to minimal in the kidney cortex. Most significantly, however, he was



able to demonstrate differences in the calcium content of anatomically comparable regions of the kidney when he compared specimens from populations with and without a tendency to form renal stones.

It is well known that calcium salts tend to be deposited in tissues which are already the seat of injury or damage or in tissues which are undergoing degeneration. Scarparelli (1960), in drawing attention to this, pointed out that the cause of damage in some cases could be an excess of calcium itself. Cells, such as those in the nephron, which are involved in the metabolism or transport of calcium are probably protected against its toxic effects within certain limits. An excess of calcium, however, may overwhelm the protective mechanism and result in tissue damage and subsequent calcium deposition.

The lesions described by Anderson (1968) and others may, therefore, be primary and stone formation, in the tubules and calyces, a secondary phenomenon due to crystallisation on a calcified nidus extruded from the epithelium of the tubules. These lesions may thus be a direct consequence of a metabolic abnormality resulting in increased intestinal absorption of calcium as has been found in such a high proportion of this series of stone formers. What the nature of this metabolic abnormality is must remain inconclusive at the moment, but I strongly suspect that it is bound up with the absorption of excess refined sugar, found in modern diet, causing renal acidosis and thus inhibiting tubular reabsorption of calcium. At the moment we are investigating the effects of various sugars on calcium absorption and the initial results are encouraging.

Finally, I think it is reasonable to conclude from the results detailed in this Chapter that stone recurrence may be diminished by

therapy directed at reducing the intestinal absorption of calcium and therefore the total calcium filtered load transported through the nephron.

CHAPTER 3

## THE ROLE OF CELLULOSE PHOSPHATE IN THE TREATMENT OF UROLITHIASIS

3.1 Introduction

The results detailed in Chapter 2 provide further support for using methods of treatment which reduces the intestinal absorption of calcium and therefore its urinary excretion in the management of recurrent urolithiasis.

Dietary measures have already been used towards this end and Nordin (1972) considers that a diet low in calcium and oxalates is the simplest and most effective approach to the treatment of renal stone. Sodium phytate has been shown to form a relatively insoluble complex with calcium in the gut and the effect of this has been to lower urinary calcium in patients with idiopathic hypercalcaemia (Henneman, et al. 1958). Further investigations of the effects of sodium phytate, however, has shown an increase in urinary phosphates concomitant with the decrease in calcium absorption (Parfitt et al. 1964). Oral administration of sodium phosphate also reduces intestinal calcium absorption and urinary excretion, but urinary orthophosphate increases at the same time. Therapeutic use of both sodium phytate and sodium phosphate is therefore accompanied by the possibility of an increase in calcium phosphate precipitation on account of the increase in its activity/product ratio (Pak et al. 1970).

The thiazides as a group reduce urinary calcium excretion and increase renal excretion of phosphate as pyrophosphate with a concomitant increase in the urinary sodium and potassium. Calcium balance studies carried out at the time of thiazide treatment suggest that calcium is retained during such treatment. (Lamberg and Kuhlback, 1959; Lichwitz et al. 1961; Higgins et al. 1964; Yendt et al. 1966;

Harrison and Rose, 1968).

Sodium cellulose phosphate, the sodium salt of the phosphoric ester of cellulose (Whatman Biochemicals Ltd) is an ion exchange cellulose with special affinity for divalent cations because of the steric configuration of the phosphate radicals attached to the cellulose molecule. In the stomach it exchanges sodium for calcium, which is eliminated in the faeces, so preventing the absorption of dietary calcium and it similarly binds secreted calcium preventing its reabsorption. The diminution in calcium absorption is accompanied by a reduction in the renal excretion of calcium and a slight increase in urinary phosphorus but the urine saturation with brushite ( $\text{CaHPO}_4 \cdot 2\text{H}_2\text{O}$ ), a probable nidus for calcium stone, is reduced Pak (1973).

This Chapter describes some observations on the effect of sodium cellulose phosphate on intestinal calcium excretion in patients with urolithiasis, along with the results of a limited clinical application of the substance.

### 3.2 Materials and Methods

The effect of cellulose phosphate was evaluated in a series of patients from the Department of Urology in this hospital in conjunction with Surgeon Captain N. J. Blacklock, consultant Urologist and head of the Department. All the patients had full general and metabolic investigation including excretion urography. Cases of overt hyperparathyroidism were excluded.

Intestinal calcium absorption was measured by the technique of external radioisotope counting described in Chapter 1. The normal range of absorption established by this method being 25 to 35 per cent of the

calcium meal.

Urinary calcium excretion was assessed with 24 hour specimens of urine by atomic absorption spectroscopy using the Unicam SP.90. Hypercalciuria was taken as the excretion of more than 300 mg of calcium per day in the male and more than 250 mg of calcium per day in the female. (Hodgkinson and Pyrah, 1958).

The serum calcium, inorganic phosphate, protein and alkaline phosphatase were estimated on at least four separate occasions at the outset and at each attendance for follow-up examination with the patient in the fasting state. Serum calcium was measured by auto-analyser using Technicon Method N3b and the upper limit of normal for this laboratory was taken as 10.5 mgms per 100 ml. Serum iron, copper and magnesium were measured in each patient initially, and subsequently at each follow-up examination. Serum iron was measured by Richterich's method and copper and magnesium by atomic absorption spectroscopy (Unicam SP.90).

### 3.3 Results

Initially the effect of sodium cellulose phosphate on  $^{47}\text{Ca}$  uptake was evaluated for varying conditions of dosage and administration. In all the tests described, with the exception of the investigation into the effect of time of administration of cellulose phosphate on calcium absorption, the cellulose phosphate was taken in water within 5 minutes of the oral dose of  $^{47}\text{CaCl}_2$  given on the second day of the absorption measurement protocol.

#### 5g dose

In 10 patients who were given 5g of the substance there was a marked reduction in  $^{47}\text{Ca}$  absorption (Table 3.1).

TABLE 3.1

Effect of cellulose phosphate on  $^{47}\text{Ca}$  absorption in cases known to absorb calcium excessively from the intestine

Subject	$^{47}\text{Ca}$ Absorption	
	Before C.P.	After C.P.
K.D.	70%	11%
T.G.H.	60%	19%
R.B.	58%	16%
E.M.F.	76%	23%
B.B.	67%	16%
T.P.	84%	26%
A.M.	57%	18%
P.G.	77%	15%
C.E.B.	77%	18%
N.J.F.	91%	32%



### Effect of varying dose

Two patients were given 1g cellulose phosphate, a further two patients 2g and a fifth patient 3g and then 5g at the appropriate time in an uptake test. The effect appeared to be closely related to the dose (Figure 3.1).

5g reduced the intestinal calcium absorption by as much as 85 per cent and even a 1g dose resulted in a 50 per cent reduction. The 5g sachet provided as the standard dose therefore has a wide margin for effective action in this respect. Such a dose, however, is probably essential when it is considered that the substance will ordinarily be dispersed throughout a semi-solid food bolus.

Urinary calcium excretion was measured concurrently with the absorption test and administration of the various doses of cellulose phosphate.

The results show an inverse relationship between both fractional calcium absorption and urinary calcium excretion and increasing doses of sodium cellulose phosphate (Figure 3.2).

### Effect of varying time of taking the cellulose phosphate

The influence on calcium absorption of taking a 5g dose of sodium cellulose phosphate at variable intervals of time from a calcium meal was evaluated (Figure 3.3).

Maximum effect was achieved if the substance was taken with a meal or within one hour thereafter. There was a marked reduction in effect if the substance was taken more than one hour afterwards. Bearing in mind that the calcium meal was in liquid form in these tests, it is likely that the dose relationship of sodium cellulose phosphate to a



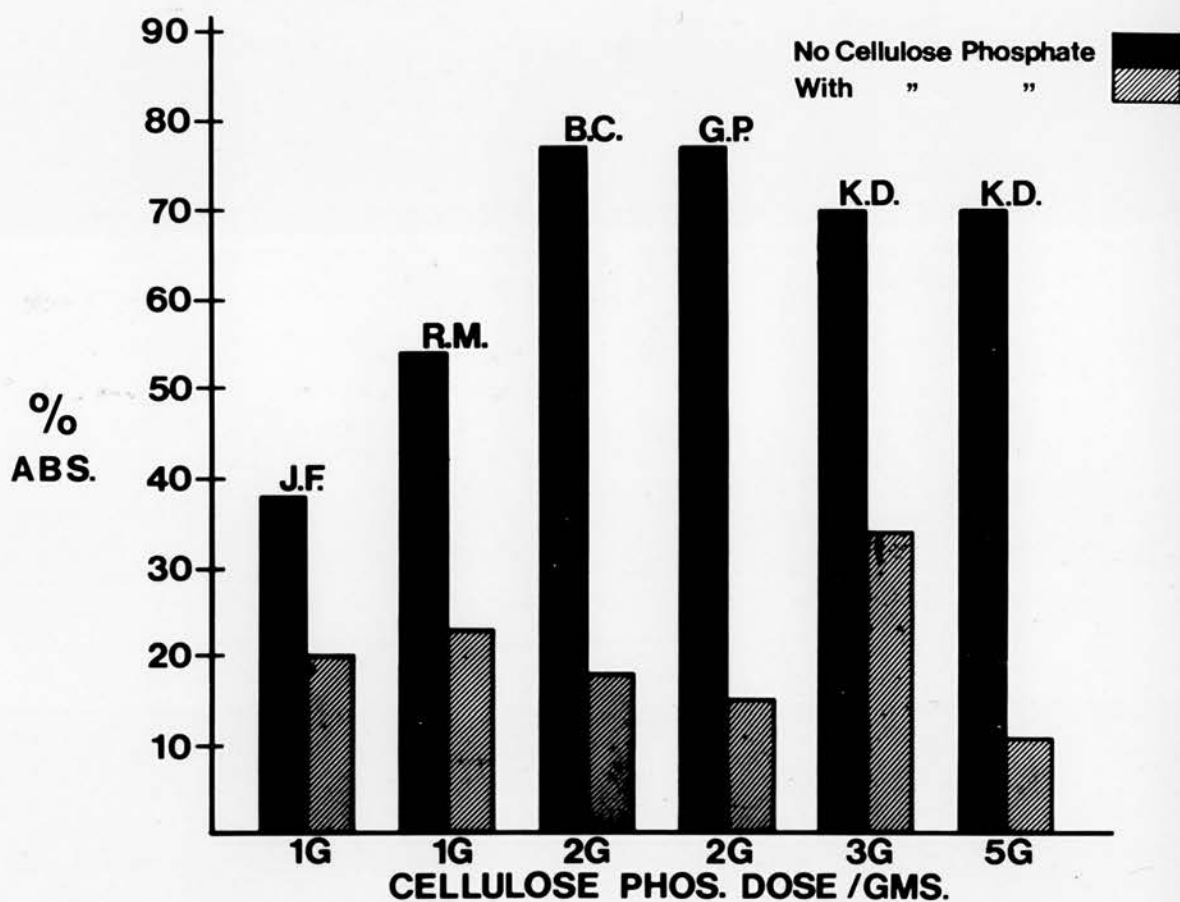


FIGURE 3.1 Effect of variable dosage of sodium cellulose phosphate on intestinal calcium absorption

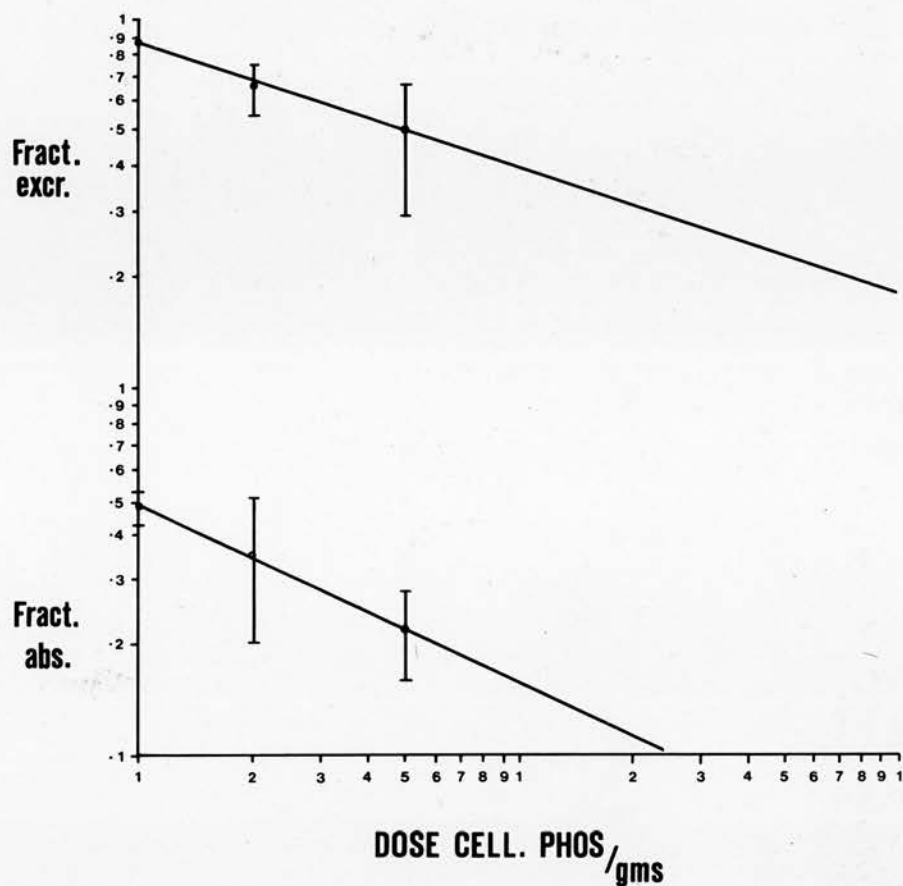


FIGURE 3.2 Comparison of the influence of varying dosage of sodium cellulose phosphate on intestinal absorption and urinary excretion of calcium

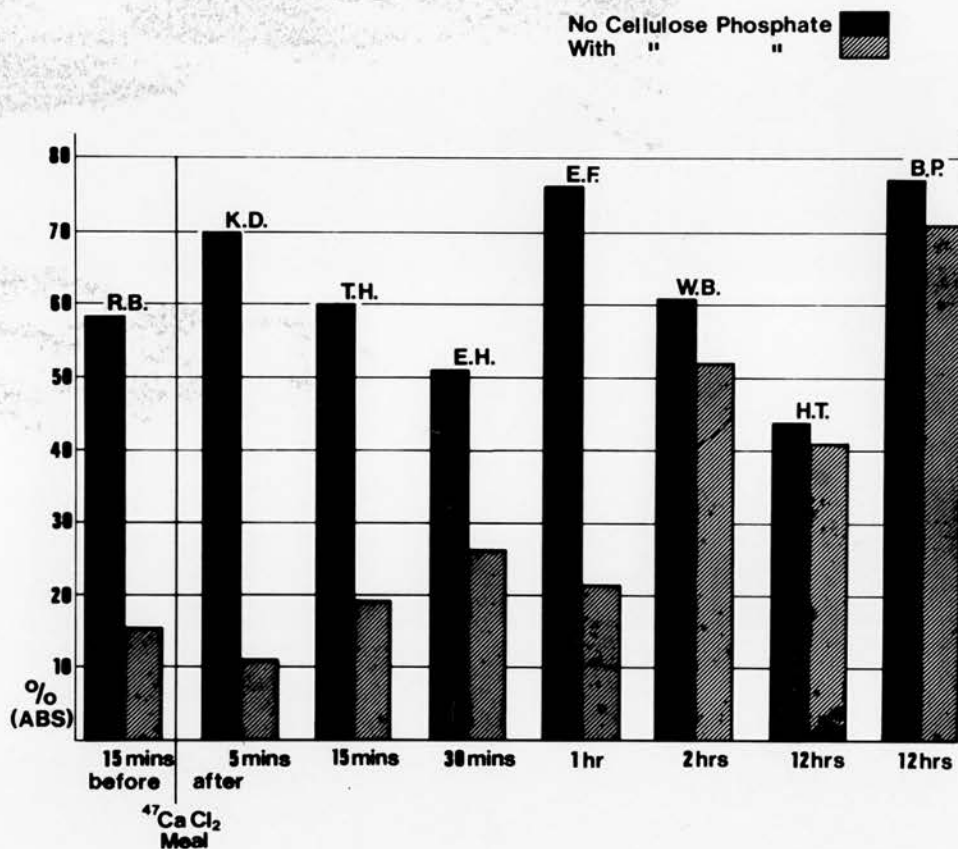


FIGURE 3.3 The influence of time between a calcium containing meal and dose of sodium cellulose phosphate on the reduction of intestinal calcium absorption

normal meal is even more critical.

#### Effect of 5g dose on urinary calcium excretion

The effect of sodium cellulose phosphate on urinary calcium excretion was assessed in a number of patients with hypercalciuria of varying degree (Figure 3.4).

In all these patients, 5g of the substance, taken 3 times daily at meal-times, effectively reduced urinary calcium excretion to within normal limits.

#### Effect of cellulose phosphate on other divalent cations

Serum levels of calcium and phosphorus were not altered in any of the patients even when cellulose phosphate had been taken for a period as long as seven years in a dose of 5g, three times daily. (Figure 3.7).

Since the action of sodium cellulose phosphate is not selective as regards the divalent cations it can absorb, there is the theoretical possibility of trace metal deficiencies in long-term usage. Dent et al. (1964) found a fall in plasma magnesium from 2.0 to 1.4 mEq/h. Pak (1973) noted a reduction in the serum concentration of magnesium and its renal excretion in a majority of cases. He found it did not significantly affect the metabolism of copper or zinc. Pietrek and Kokot (1973) noted a trend towards reduction in the levels of serum magnesium, iron, copper and zinc concentrations although this was not statistically significant.

In the series of patients investigated in this report who were treated with cellulose phosphate, without magnesium supplement, for various periods of time there appears to have been little significant effect on plasma magnesium (Figure 3.5). One case treated for more than 4 years has a serum magnesium of 2.2 mg/100 ml. another treated for a

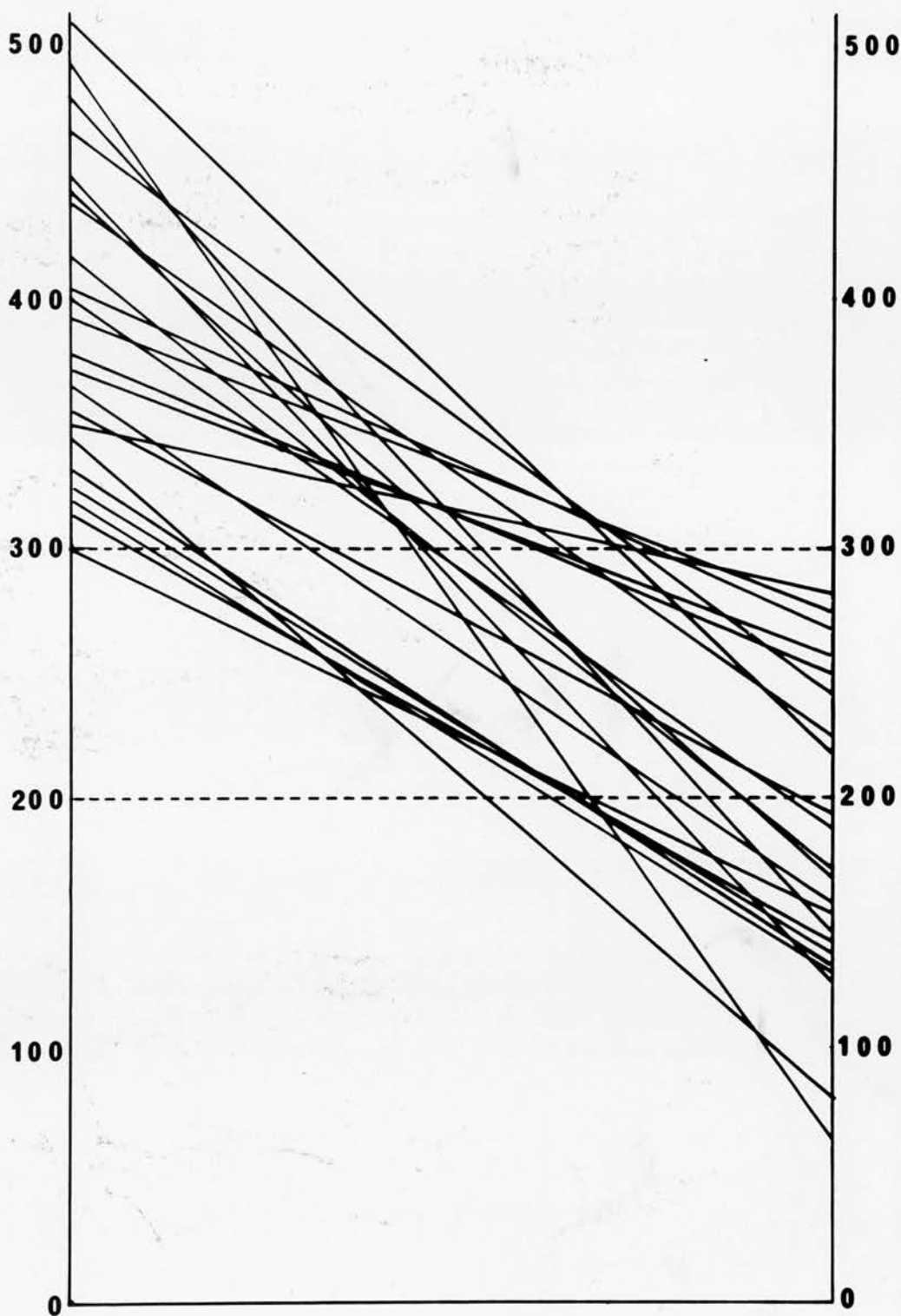


FIGURE 3.4 Effect of sodium cellulose phosphate on urinary calcium excretion in 22 cases of idiopathic hypercalciuria and stone formation.

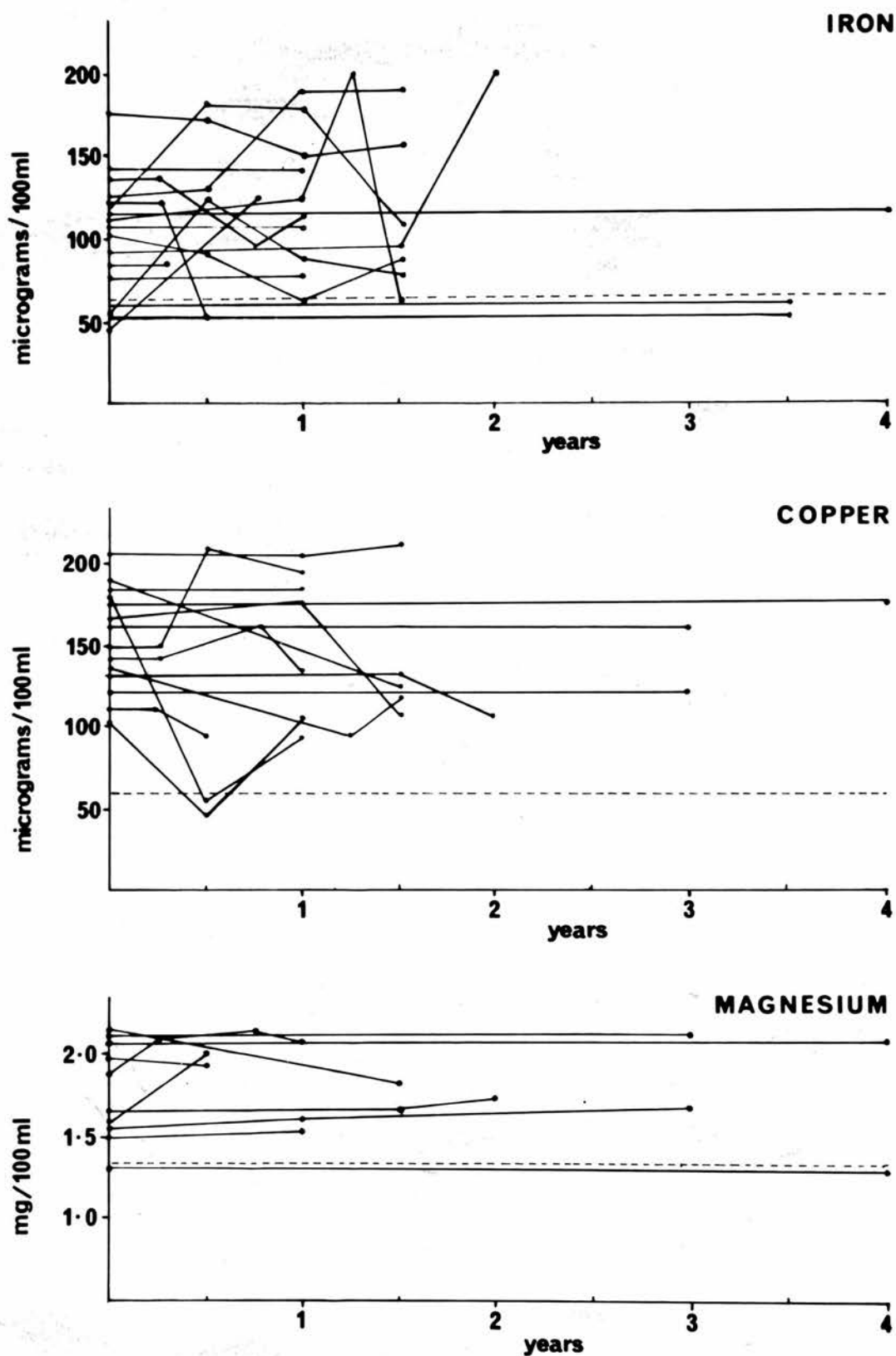


FIGURE 3.5 Variation in serum levels of iron copper and magnesium with long term sodium cellulose phosphate treatment.

similar period however, has a level of 1.4 mg/100 ml.

Serum copper and iron appears to have been largely uninfluenced. In two cases who have been taking cellulose phosphate for more than three years the serum iron at present is 50 and 60 mg/100 ml. respectively, the lower level of normal. (Figure 3.5).

#### Clinical evaluation of Sodium Cellulose Phosphate in recurrent Calcium Urolithiasis

All cases treated with sodium cellulose phosphate had a history of recurrent urolithiasis and were hypercalciuric. The duration of treatment up to the present time is variable, ranging from some months to several years.

Sodium cellulose phosphate in our experience is easy to take and is quite palatable. Intestinal upset and diarrhoea which had been noted by others (Rose and Harrison, 1972) have not been encountered.

The urinary calcium excretion was measured in a number of patients at various intervals of time from the time of commencing treatment. (Figure 3.6).

In two patients, hypercalciuria persisted but a subsequent satisfactory reduction in calcium excretion followed supplementing the treatment with a low calcium diet. One of these cases had a  $^{47}\text{Ca}$  uptake of 70 per cent. The majority show a satisfactory reduction of calcium excretion to within normal rates.

Pietrek and Kokot (1973) have found the urinary calcium to be consistently maintained at reduced levels when using cellulose phosphate but others (Harrison and Rose, 1972) have had the impression that the initial reduction is not maintained. This is probably a measure of the



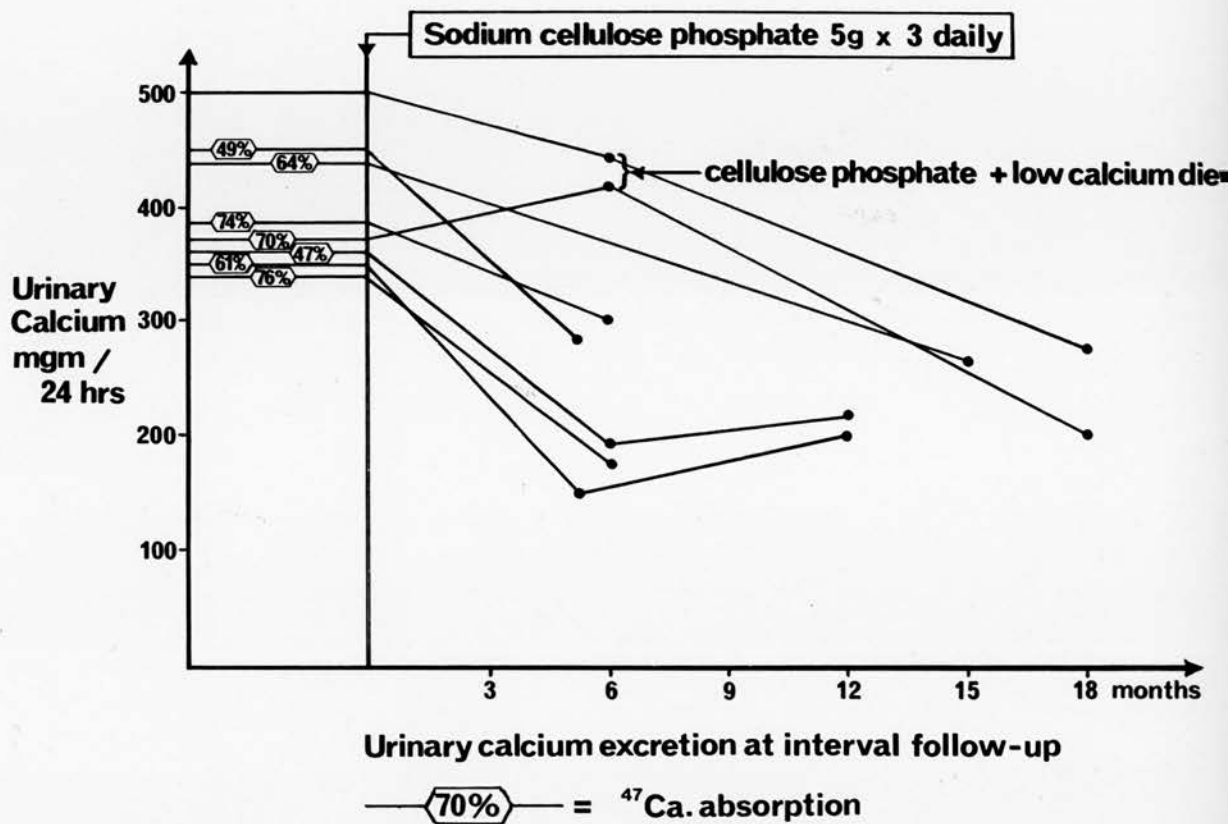


FIGURE 3.6 Urinary calcium excretion at various intervals from commencement of treatment with sodium cellulose phosphate

tendency to default with treatment after a time rather than an indication of the development of resistance in some form to its effect.

Both Pak (1973) and Pietrek and Kokot (1973) already have some evidence of a reduced frequency of stone incidence with this treatment. The effect of the preparation in a number of patients in the series reported here, who have been treated for several years, is shown graphically. (Figure 3.7).

Only 2 new stones have been formed in the 9 cases depicted. In both of these there was an additional aggravating factor of service in a tropical climate at the time of the recurrence and both were engaged on watchkeeping duties at sea when there was difficulty in relating cellulose phosphate dosage to irregular meals. Case P.H. has shown the most significant response. This patient had consistently formed several stones annually from 1958 until the time of starting treatment with sodium cellulose phosphate in 1969. The majority of stones passed had been calcium oxalate but several were "mixed". Since treatment was started there has been no further instance of urinary colic or passage of a stone, and his urinary tract is demonstrably clear of opaque calculi at the present time. No other therapy or dietary means of control has been adopted by this patient in the meantime.

### 3.4 Discussion

In Chapter 2 the significance of excessive intestinal calcium absorption and hypercalciuria in a high proportion of recurrent stone formers was discussed. The results provided further support for a rationale of treatment directed at reducing intestinal calcium absorption and through this, the renal filtered load of calcium and urinary calcium excretion.

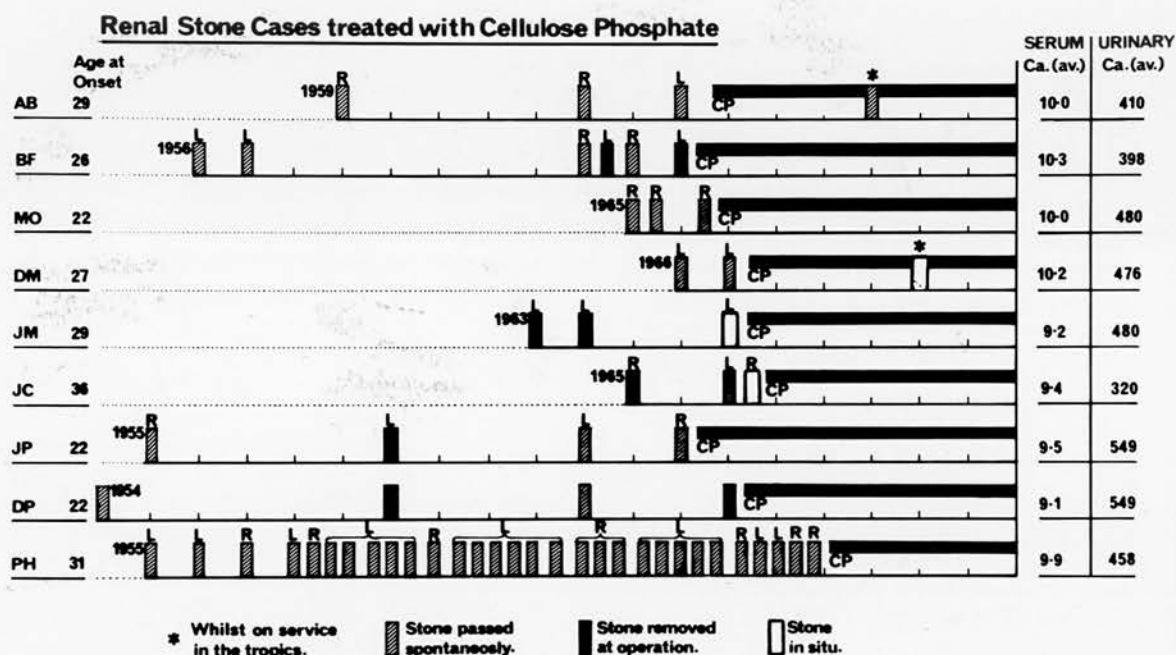


FIGURE 3.7 Graphic representation of stone incidents in 9 cases both before and after the commencement of sodium cellulose phosphate treatment

This may be affected in whole or in part by dietary control and Nordin (1972) has described a low calcium, low oxalate diet as the simplest and most effective regime. Dietary control, however, whilst being an ideal form of management in a metabolic unit poses formidable problems to the patient in the home and working conditions, especially when circumstances necessitate meals away from home as when travelling, and when feeding is institutional. In these circumstances there is a need for an effective agent to reduce the absorption of ingested calcium. Sodium cellulose phosphate is demonstrably effective in this respect and so far has proved innocuous. It is considered that there is a case for its use, suitably monitored, in cases of recurrent urolithiasis who have been shown to absorb calcium excessively from the intestine and to be hypercalciuric.

We have investigated other agents effective in removing calcium from the diet in an insoluble bound form and thus eliminating it in the faeces. As mentioned in Chapter 2 we are currently investigating the effect of refined sugars on calcium absorption and the implications are that these sugars are involved in the evident increase in urolithiasis and hyperabsorption of calcium in the industrial highly developed countries of the world. It may well be that the ability of sodium phytate to bind calcium and prevent its absorption (Henneman et al. 1958), and the low consumption of refined carbohydrates are major factors in the evident low morbidity due to renal stone in populations of less developed and agricultural countries with high intake of wholemeal products, such as bran or oatmeal, in their diet eg. the Highlanders of Scotland.

While it has been shown by Parfitt et al. (1964) that sodium phytate increases the amount of urinary phosphates, thus apparently negating the benefits of reduced calcium absorption, the overall beneficial effect of

wholemeal products in combating the suspected and evident defects in absorption and diet, due to excess of refined sugar, is becoming more obvious. This is not confined solely to urolithiasis but is increasingly recognised in the aetiology and treatment of a multiplicity of gastrointestinal disorders today.

Whatever the outcome of this work in progress, it is evident from the results detailed in this Chapter that sodium cellulose phosphate is a useful and safe preparation in the treatment of recurrent urolithiasis and hypercalciuria.

CHAPTER 4

## CALCIUM ABSORPTION IN HYPERPARATHYROIDISM

4.1 Introduction

In any series of patients investigated for renal stone one of the main features is hypercalciuria (Flocks, 1939; Hodgkinson and Pyrah, 1958). The phenomenon of hypercalciuria with an associated tendency to hypophosphatemia and a normal serum calcium was described as the syndrome of idiopathic hypercalciuria by Albright et al. (1953) and Henneman et al. (1958), Peacock et al. (1967) confirmed these observations and suggested that the intestinal absorption of calcium was increased in most patients. In Chapter 2 in a detailed investigation of 125 cases of urolithiasis it is shown that 82 per cent of patients were absorbing calcium excessively from the intestine thus supporting Peacock's findings. When this is considered along with the results of cellulose phosphate therapy shown in Chapter 3 it would tend to indicate that a primary abnormality in intestinal absorption, probably related to the absorption of refine sugars, was responsible for the increased calcium absorption.

Patients with idiopathic hypercalciuria may show some of the biochemical abnormalities found in those with primary hyperparathyroidism presenting with renal stone. The urinary calcium is commonly raised in primary hyperparathyroidism and hypophosphatemia while reduced renal tubular reabsorption of phosphate is found in both conditions (McGeown, 1957). Usually in primary hyperparathyroidism the serum calcium is increased but this is not a consistent finding as has been shown by Yendt and Gagne (1968) and Wills et al. (1969).

Since abnormalities of calcium and phosphorus metabolism are common to both patients with idiopathic hypercalciuria and those with primary hyperparathyroidism presenting with renal stone it may be agreed that

the pathological basis for such abnormalities is the same in both conditions. It was suggested by Albright et al. (1953) that the changes found in phosphorus metabolism in patients with idiopathic hypercalciuria were due to parathyroid overactivity. They stated that this was secondary to hypercalcaemia caused by excessive loss of calcium in the urine due to a primary abnormality in the renal tubular handling of calcium. Other workers however, have shown that in idiopathic hypercalciuria the serum calcium concentration tends toward the upper limit of normal (Peacock et al. 1968) and that the renal tubular reabsorption of calcium is generally normal in these patients (Peacock and Nordin, 1968).

Adams et al. (1970) were able to demonstrate hypercalcaemia in 8 out of 19 patients with idiopathic hypercalciuria following provocative tests of parathyroid activity based on phosphate deprivation and the administration of chlorathiazide. Subsequent exploration of the neck on five out of these eight patients with hypercalcaemia showed four of them to have parathyroid adenomas and the fifth patient had 'normal glands' but responded satisfactorily to subtotal parathyroidectomy.

That increased calcium absorption in patients with idiopathic hypercalciuria presenting with renal stone is a primary phenomenon, rather than secondary to increased losses of calcium in the urine, is amply demonstrated in Chapter 2 of this work and supported by the findings of others (Henneman et al. 1958; Harrison, 1959; Peacock et al. 1968).

It has also been shown by Wills et al. (1970) that the parathyroids play a small but significant role in the gastro-intestinal absorption of calcium. They found that in six normal subjects and in one patient with idiopathic hypoparathyroidism there was a small increase in calcium absorption from the gut during the administration of parathyroid extract.



In a series of patients with urolithiasis who were investigated in this Department during the period January 1970 until September 1973 a certain number were found to be hypercalcaemic and were therefore excluded from the 125 cases whose detailed investigations are described in Chapter 2 of this work. This Chapter describes some observations made on these patients and others, referred from the metabolic unit of Southampton General Hospital with hypercalcaemia, and compares them with a control group and patients with normocalcaemic recurrent nephrolithiasis.

#### 4.2 Materials and Methods

Fifteen patients were referred to this department for investigation of hypercalciuria with and without renal stones and in whom primary hyperparathyroidism was suspected. A comparison was made between these patients, a group of 47 patients with recurrent urolithiasis whose serum calcium measurements were within normal range, and 20 control subjects who had no apparent abnormalities of calcium metabolism.

All the patients from these three groups had their serum calcium and inorganic phosphate measured on at least four separate occasions. Their 24 hour urinary calcium was measured by atomic absorption spectrophotometry (Unicam SP.90). Urinary cyclic AMP (adenosine 3':5' - monophosphoric acid) was estimated using the standard Amersham radio-immunoassay kit based on the protein binding assay of Gilman (1970) and the results expressed as  $\mu\text{mol/g}$  creatinine. Serum parathyroid hormone was estimated in collaboration with Dr Buckle of the Metabolic Unit, Southampton General Hospital using a modification of the radio-immunoassay technique detailed by Arnaud et al. (1971).

Following these investigations 12 of the 15 patients had neck explorations and subsequent sub-total parathyroidectomy for parathyroid adenoma in ten cases and parathyroid hyperplasia in the remaining two.

Intestinal calcium absorption was measured in all patients and controls by the arm counting method detailed in Chapter 1. The 12 patients who had sub-total parathyroidectomy performed had their calcium absorption measured subsequent to the operation in order to compare the pre and post operative calcium uptake.

### 4.3 Results

#### Serum Calcium and Phosphorus

Measurements of serum calcium and phosphorus in all 20 control subjects showed a mean serum calcium of  $9.82 \pm 0.51$  mg/100 ml. and a mean serum phosphorus of  $3.72 \pm 0.64$  mg/100 ml. (Table 4.1). In no subject was the serum calcium greater than 10.5 mg/100 ml. or the serum phosphorus less than 2.6 mg/100 ml. the upper limit for serum calcium and the lower limit for serum phosphorus for this laboratory.

In the 15 patients with suspected primary hyperparathyroidism serum calcium was greater than 10.5 mg/100 ml. in 12 cases and within the normal range in the remaining three. The mean value was significantly raised at  $11.62 \pm 0.42$  mg/100 ml. The mean serum phosphorus for this group was  $2.74 \pm 0.42$  mg/100 ml. significantly lower than that for the control group. In the 47 patients with recurrent urolithiasis both mean serum calcium and serum phosphorus were within normal limits, and in no case was the serum calcium above 10.5 mg/100 ml. or the serum phosphorus below 2.6 mg/100 ml.

#### 24 hour urinary calcium (Table 4.1)

24 hour urinary calcium measurements on control subjects showed a mean excretion of  $164 \pm 44$  mg/24 hours. In no subject was the urinary calcium greater than 250 mg/24 hours. In the primary hyperparathyroid group the mean calcium excretion was  $458 \pm 54$  mg/24 hours and in all cases was significantly raised above the normal upper limit of 300 mg/24

TABLE 4.1

In each group of patients the results are present as the mean  $\pm$  S.D. of the mean values from individual patients

	Number of Patients	Mean serum calcium mg/100 ml.	Mean serum phosphorus mg/100 ml.	Mean urinary calcium mg/24 hrs.	Mean urinary cyclic AMP $\mu$ mol/g Cr	Mean serum Parathormone $\mu$ g.eq/ml.	Mean $^{47}$ Ca absorption % of oral meal
Primary Hyperparathyroidism	15	11.58 $\pm$ 0.60	2.74 $\pm$ 0.42	458 $\pm$ 54	8.08 $\pm$ 2.51	1.92 $\pm$ 1.03	64 $\pm$ 19
Normocalcaemic recurrent urolithiasis	47	9.73 $\pm$ 0.38	3.51 $\pm$ 0.45	346 $\pm$ 104	3.64 $\pm$ 0.7	0.31 $\pm$ 0.23	56 $\pm$ 16
Control subjects	20	9.82 $\pm$ 0.51	3.72 $\pm$ 0.64	164 $\pm$ 44	4.12 $\pm$ 0.62	0.40 $\pm$ 0.28	30 $\pm$ 6

hours for this laboratory.

The patients with recurrent urolithiasis showed a mean urinary calcium of  $346 \pm 104$  mg/24 hours again significantly raised above normal in 42 cases and within normal limits in the remaining 5.

#### Urinary cyclic AMP (Table 4.1)

In the control group urinary cyclic AMP was less than  $5 \mu\text{mol/g}$ . creatinine with a mean value of  $4.12 \pm 0.62 \mu\text{mol/g}$ . creatinine. Among patients with primary hyperparathyroidism the mean value for urinary cyclic AMP was  $8.34 \pm 2.58 \mu\text{mol/g}$ . creatinine, significantly higher than in the control group. The mean value for the patients with recurrent urolithiasis was  $3.64 \pm 0.7 \mu\text{mol/g}$ . creatinine slightly less than on the control group.

#### Serum parathormone (Table 4.1)

Among the control subjects radioimmuno assay of serum parathormone gave a mean value of  $0.40 \pm 0.28 \mu\text{g eq/ml}$ . Patients with hyperparathyroidism showed a mean value of  $1.74 \pm 0.31 \mu\text{g eq/ml}$ . In 12 out of the 15 patients serum parathormone was greater than  $1 \mu\text{g eq/ml}$  which is the accepted upper limit of normal for this technique. The patients with recurrent urolithiasis showed a mean of  $0.31 \pm 0.23 \mu\text{eq/ml}$  and none of these patients had a serum level above  $0.34 \mu\text{g eq/ml}$ .

#### Intestinal $^{47}\text{Ca}$ absorption (Table 4.1)

Mean calcium absorption expressed as percentage absorption of a measured oral dose of  $^{47}\text{CaCl}_2$  among control subjects was  $30 \pm 6$  per cent of the oral dose. Patients with recurrent urolithiasis had a mean absorption of  $56 \pm 16$  per cent showing a significant increase in

intestinal calcium uptake. The hyperparathyroid group with a mean calcium absorption of  $64 \pm 19$  per cent of the oral dose, were also significant calcium hyperabsorbers.

With these results favouring a biochemical diagnosis of hyperparathyroidism in at least 12 of the suspected group of 15, it was decided to surgically explore the 12 most likely cases. Of these 12 patients 10 proved to have parathyroid adenomas and in the remaining two parathyroid hyperplasia was demonstrated. Following sub total parathyroidectomy a satisfactory reduction in hypercalciuria and intestinal calcium absorption was immediately apparent. Measurements of  $^{47}\text{Ca}$  absorption pre and post operatively are detailed in Table 4.2.

Further examination of the results in patients with hyperparathyroidism shows good correlation between urinary cyclic AMP and serum parathormone (correlation coefficient = 0.875) (Figure 4.1). Comparisons of serum calcium with urinary cyclic AMP (Figure 4.2) and serum parathormone (Figure 4.3) show most measurements to lie outside the normal range but without an apparent relationship.

There was no obvious correlation between intestinal calcium absorption and urinary cyclic AMP or serum parathormone.

#### 4.4 Discussion

Hypercalciuria is frequently the most consistent feature of hyperparathyroidism and is the hallmark of idiopathic hypercalciuria. In this work another common factor became apparent in that intestinal hyperabsorption of calcium in 82 per cent of patients with urolithiasis and in all the patients referred for parathyroid investigation became obvious. The hyperabsorption of hyperparathyroidism is recognized as being secondary to excessive calcium loss in the urine and the expression

TABLE 4.2

Results of calcium absorption measured by external radioisotope counting before and after sub-total parathyroidectomy

Subject	$^{47}\text{Ca}$ Absorption before operation % of $^{47}\text{Ca}$ meal	$^{47}\text{Ca}$ absorption after operation % of $^{47}\text{Ca}$ meal
I.P.	83	23
G.B.	79	39
R.B.	63	34
H.S.	55	30
R.P.	43	23
D.B.	76	35
C.C.	42	25
R.S.	60	26
I.R.	61	28
B.K.	54	25
J.W.	69	28
I.J.	83	34

**FIG 4.1** Correlation of Urinary cAMP with Serum Parathormone  
in patients with hyperparathyroidism.

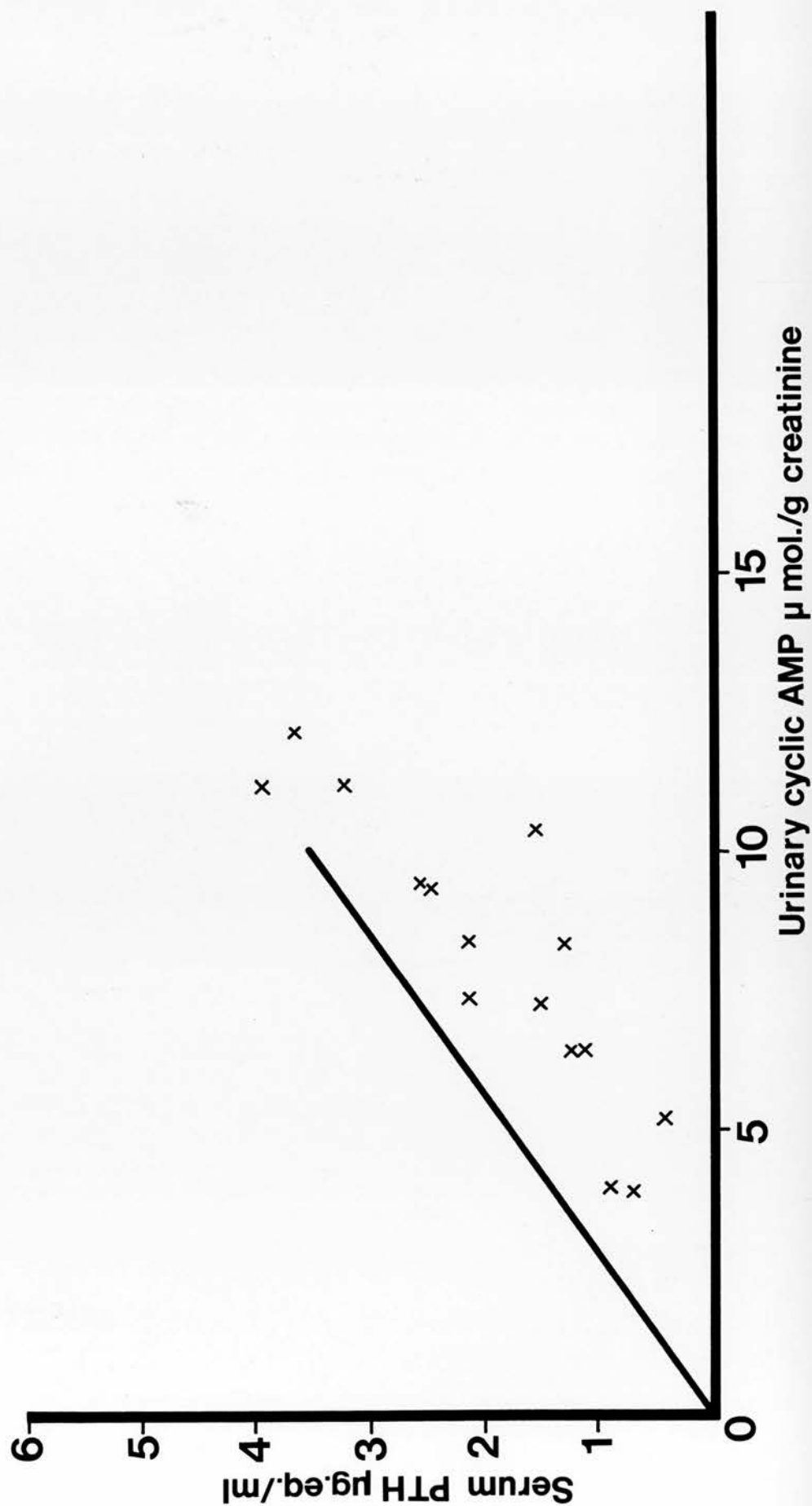
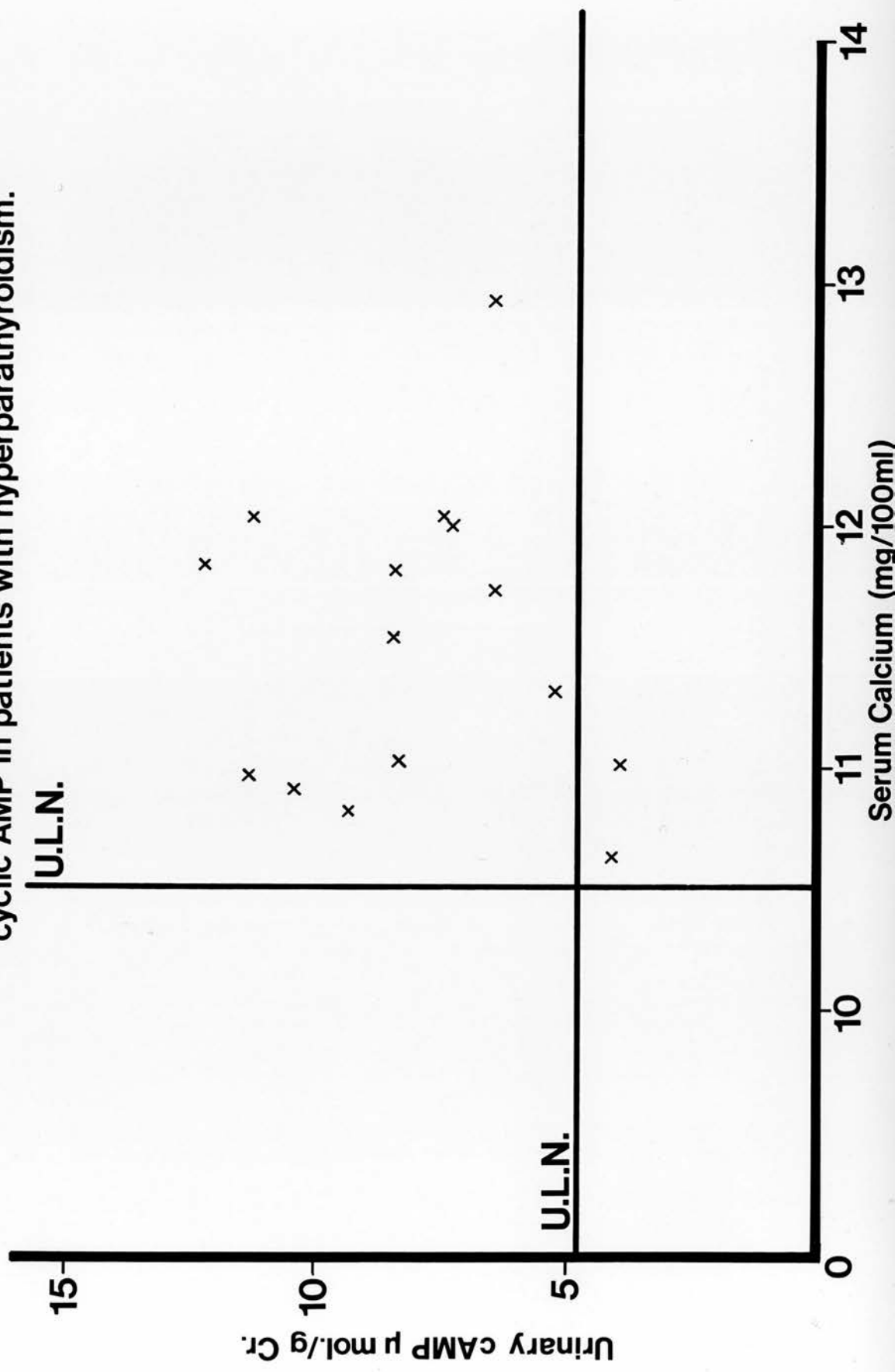
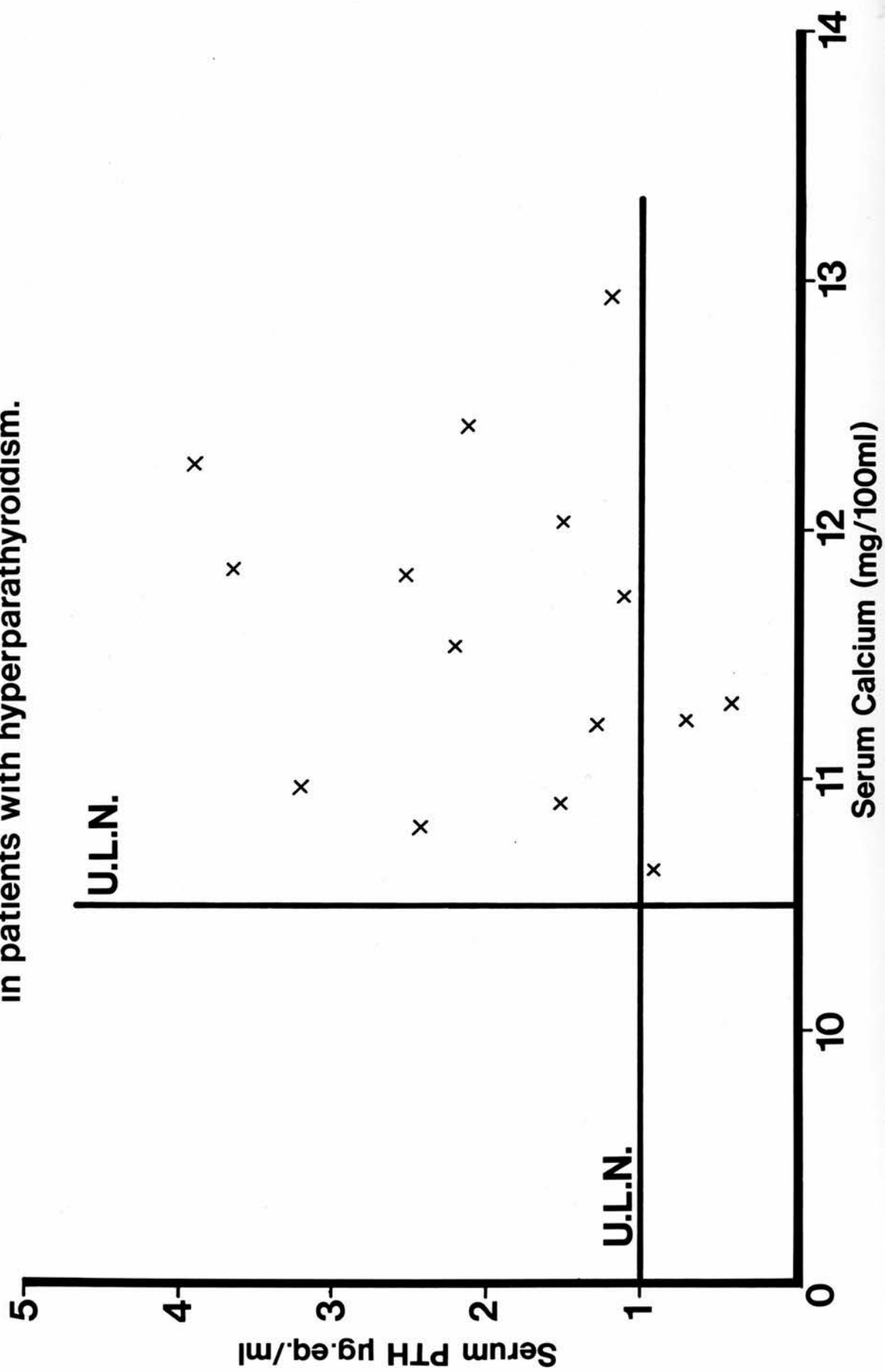




FIG 4.2 Comparison between Serum Calcium and Urinary cyclic AMP in patients with hyperparathyroidism.



**FIG 4.3 Comparison of Serum Calcium with Serum PTH in patients with hyperparathyroidism.**



'resorptive hypercalciuria' has been used to describe this because of the frequent association with excessive skeletal resorption (Nordin, Peacock and Wilkinson, 1972). The hypercalciuria encountered in 77 per cent of the recurrent urolithiasis group discussed in Chapter 2 is due to a primary increase in calcium absorption from the intestine and could correspondingly be called an 'absorptive hypercalciuria'. This observation has been supported by other workers (Norden et al. 1972; Pak et al. 1972 and Pak, 1973). The importance of a third possible cause of hypercalciuria due to excessive carbohydrate intake is currently being investigated by us, the theory being that excess absorption of refined sugars in modern diet causes a renal tubular acidosis thus inhibiting tubular reabsorption of calcium. Other workers (Pak, 1973; Coe et al. 1973) have commented on this 'renal leak' hypercalciuria and have associated it with secondary hyperparathyroidism.

In practical terms the differentiation between primary hyperabsorption of calcium and secondary hyperabsorption due to parathyroid induced hypercalciuria is imperative since optimal treatment depends on the exact aetiology. In this Chapter an attempt to indicate the differences between the two types of hyperabsorption has been made, resulting in the successful diagnosis of 12 cases of hyperparathyroidism, confirmed at operation. In contrast the patients with recurrent urolithiasis were appropriately treated with sodium cellulose phosphate, as detailed in Chapter 3, to directly inhibit intestinal absorption of calcium.

In comparing the patients with hyperparathyroidism with those exhibiting recurrent urolithiasis both groups showed excessive intestinal calcium absorption and 24 hour urinary excretion as compared to the control group. Both the mean calcium absorption and mean urinary calcium

excretion, however, were higher in the primary hyperparathyroid group when compared with patients with recurrent urolithiasis. These groups differed in that the mean serum calcium, the mean urinary cyclic AMP and the mean serum parathormone were significantly above the recognised upper limits of normal in those patients with hyperparathyroidism and in that there was a significant relationship between urinary cyclic AMP and serum parathormone in the hyperparathyroid group. The patients with recurrent urolithiasis or 'absorptive hypercalciuria', on the other hand, had mean serum calcium and parathormone and the mean urinary cyclic AMP within normal limits. A further difference was evident in measurements of the serum phosphorus concentration in that the hyperparathyroid group showed levels significantly lower than those found in both recurrent urolithiasis and control groups.

It appears from this that patients who, in addition to the common features of hypercalciuria and excessive intestinal calcium absorption found in the 'absorptive' and 'resorptive' types of idiopathic hypercalciuria, exhibit a raised serum calcium and serum parathormone, a raised urinary cyclic AMP and a lowered serum phosphorus must be regarded as suffering from hyperparathyroidism and elective surgery seriously considered. Those patients who exhibit excessive intestinal absorption and urinary excretion of calcium only are 'absorptive' hypercalciurics and should be treated by reducing their calcium absorption with a low calcium diet or by administering calcium inhibitors such as sodium cellulose phosphate.

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## APPENDIX A

## MEASUREMENT OF ORAL CALCIUM ABSORPTION FROM THE GUT BY EXTERNAL ISOTOPE COUNTING

By Murdoch A. Macleod

### ABSTRACT

Among the factors which regulate normal gastro-intestinal calcium absorption, current thought recognises calcium intake, vitamin D and parathyroid hormone as playing an important part. It is well documented that gastro-intestinal calcium absorption is reduced in states of mal-absorption, hypoparathyroidism and in patients with chronic renal failure, and raised in states of hyperparathyroidism, urolithiasis and idiopathic hypercalcaemia.

Difficulties inherent in classic calcium-balance techniques have prompted a search for more practical and reliable methods of measuring the degree of impairment of calcium absorption. This paper describes a study of intestinal calcium absorption in 10 normal subjects and four patients, with various disorders of calcium metabolism, using an external radio-isotope counting technique.

### Introduction

During the past decade, interest in calcium metabolism has greatly expanded and with current methods of measurement of calcium absorption, both time consuming and requiring hospitalisation with strict metabolic regimen, a simple more direct method would be of great advantage. Measurement of serum calcium alone will only give the equilibrium figure between calcium input into the bloodstream (net absorption and bone resorption) and calcium output (bone mineralisation and renal excretion) at the time of measurement and will not necessarily reflect quite large changes in any one of these parameters. For example, the concept that there exists a 'steady state' or physio-chemical equilibrium between blood and bone calcium, the level of which is determined by parathyroid activity, is not supported by recent work (Nordin and Peacock, 1969). The technique developed here, based on the work of Curtis, Fellows and Rich (1967) is simple, does not inconvenience the patient and only requires a few minutes of time on each of three consecutive days to perform. This method is based on the assumption that the distribution in the body of an absorbed part of an oral dose of calcium is identical to that of an entire intravenous dose, thus the fraction of a known IV dose measured in the forearm in this case, will be the same as that of an absorbed dose. Knowing the exact amount of the isotope given orally, it is then easy to calculate the exact amount absorbed from the gut.

### Materials and Method

Initial studies were carried out on eight volunteer subjects from the medical staff of the Institute of Naval Medicine who had no evident disorders of calcium metabolism or intestinal function. The isotope used was  $\text{Ca}^{47}$  a 1.31 Mev  $\gamma$  emitter with a 4.53 day half-life. The forearm being relatively small and freely mobile is especially suited to external counting and was used in all measurements. Preliminary studies showed that it took approximately 24 hours for a small IV dose of  $\text{Ca}^{47} \text{Cl}_2$  to reach equilibrium in the tissues, bone and blood. Decay from



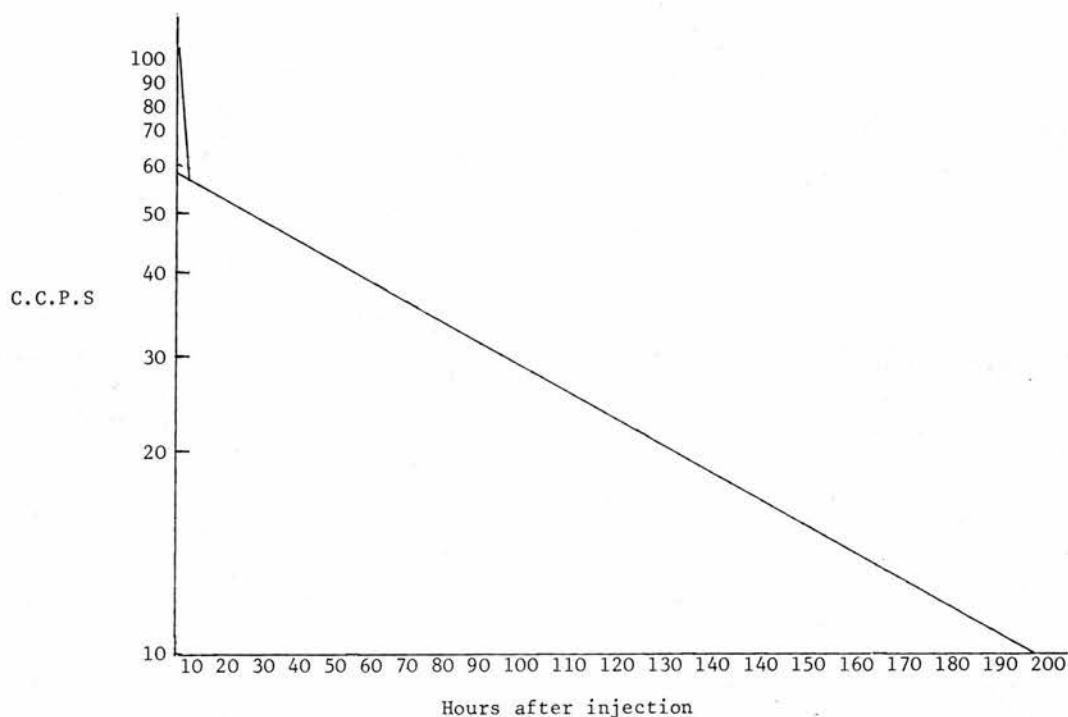


Fig 1.  $\text{Ca}^{47}$  decay in the forearm following IV injection.

that time onwards being exponential, 24 hours was selected as a suitable time at which to measure arm activity.

The apparatus used to carry out arm activity measurements comprised a large volume lead chamber incorporating two NaI (Tl) 4 inch scintillation crystals in apposition with a curved plastic arm rest and hand grip between them, to ensure constant geometry when counting the forearm on subsequent days. Counts were recorded on an Ortec timer/scaler.

On the first day, preliminary control arm background counts were made on all subjects. Each was then given  $1 \mu\text{Ci } \text{Ca}^{47} \text{Cl}_2$  in 1 ml saline IV. On day two, *ie*, 24 hours after the injection, the background count rate was measured with the subject in position beside the chamber, but with his arm outside. Following this count, the forearm was inserted into the chamber and counted for 100 seconds. On completion, each subject was given to drink  $10 \mu\text{Ci } \text{Ca}^{47} \text{Cl}_2$  in 100 mg calcium gluconate solution made up to 100 ml with water. Subjects fasted at least 12 hours before and two hours after this oral dose.

On the third day, 26 hours after the oral dose on the second day, *ie*, two hours for complete absorption of the oral dose from the intestine in the fasting patient plus the 24 hours required to achieve equilibrium, background count rate was again established and arm count rate subsequently measured. A similar final measurement was made on day four, 50 hours after the oral dose.

## Results

Arm count rate corrected for arm background and decay is expressed as arm activity (A), measured at 24 hours after injection ( $A_1$ ), 26 hours after the oral dose ( $A_2$ ), and 50 hours after the oral dose ( $A_3$ ). The ratio, intravenous dose to oral dose  $\frac{IV}{10}$  is constant and the biological decay for a 24 hour period can be expressed as the fraction  $\frac{A_3}{A_2}$ . From these measurements, it can be shown algebraically that the absorbed fraction (F) of the oral dose is,

$$F = \left( \frac{A_2}{A_1} - \frac{A_3}{A_2} \right) \left( \frac{IV}{10} \right)$$

The results obtained from the 10 normal subjects gave parameters of amounts of calcium absorbed from the gut of 25 per cent — 32 per cent ( $\pm 2.5$  per cent) with a mean of 28.5 per cent (see Table I).

Table I

Subject	$A_1$ cc/100 sec	$A_2$ cc/100 sec	$A_3$ cc/100 sec	IV/10	Absorbed Fraction 'F'	% Absorption
R.M.	3,490	16,500	14,540	0.08	0.32	32
I.L.	3,200	14,330	11,500	0.08	0.30	30
H.G.	2,270	9,600	8,016	0.08	0.28	28
D.M.	2,680	9,840	7,600	0.1	0.30	30
R.L.	3,250	12,100	9,680	0.08	0.26	26
P.C.	2,980	12,500	10,030	0.08	0.28	28
D.S.	3,950	16,800	13,500	0.08	0.29	29
P.B.	3,500	13,610	10,900	0.08	0.25	25
I.L.	2,800	10,400	8,500	0.1	0.29	29
P.G.	3,840	15,200	13,500	0.1	0.31	31

This compares favourably with a mean calcium absorption of 26.5 per cent in a similar study carried out by Curtis *et al* (1967) on 12 normal subjects who had conventional stool calcium estimations carried out at the same time giving a calculated mean calcium absorption of 25.1 per cent.

Approximately 50 measurements of calcium absorption have now been carried out on hypo and hyper-calcuric patients, with and without urolithiasis and it is hoped to present the findings in these cases at a later date. Table II shows results obtained from a sample of these patients.

Table II

Patient	Diagnosis	$A_1$	$A_2$	$A_3$	Absorbed Fraction 'F'	% Absorption
D.K.	Urolithiasis	1,650	15,800	14,200	0.70	70
R.B.	Idiopathic Hypercalcuria	1,410	8,700	8,500	0.52	52
J.L.	Hypoparathyroid	2,250	7,200	7,100	0.18	18
P.H.	Iatrogenic Hypercalcuria	1,260	8,500	7,300	0.59	59

## Discussion

The method of measuring calcium absorption from the gut described here fulfils the proposed criteria, being simple and quick to perform with minimum inconvenience to the patient. It also avoids the inaccuracy introduced in the stool collection method by the excretion

of previously absorbed calcium by the lower colon. Sources of error inherent in the technique lie in the prior assumptions and the experimental conditions obtaining. Among these are the assumption that the oral dose is maximally absorbed within two hours of administration but there is now ample evidence that, in a fasting patient, under the conditions of the test, absorption is rapid and essentially complete at two hours (De Grazia, Ivanovitch, Fellows and Rich, 1965; Avioli, McDonald, Singer and Henneman, 1965). There is a considerable amount of isotope remaining in the gut at the time of counting, 26 and 50 hours after the oral dose, but, with correct positioning of the patient in relation to the chamber, *ie*, close against the lead wall so that no part of the body is seen through the port by the detectors, and careful background counting, the effect of this surplus radioactivity in the gut can be minimised.

The principal advantage which recommends this external counting method is its simplicity. Uncertainty regarding complete stool and urine collection and accuracy of the meticulous laboratory techniques is avoided and the patient is not embarrassed or inconvenienced. The method deserves consideration as a routine laboratory investigation.

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## Calcium-47 Absorption in Urolithiasis

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An association between high urinary calcium and calcium urolithiasis was described by Flocks in 1939 but subsequent work has fallen short of establishing the exact relationship between these 2 phenomena. In a group of patients forming calcium-containing renal stones, Melick and Henne-man (1958) found that 32% had hypercalciuria. Similar findings have been made by others. Whilst an excessive urinary calcium is present in other specific diseases, hypercalciuria as a phenomenon occurring in the absence of any of these was described by Albright *et al.* (1953). This syndrome of idiopathic hypercalciuria was defined as the occurrence of a high urinary calcium in association with normal serum calcium, a tendency to hypophosphataemia and renal stone formation and it has since been recognised by others.

Caniggia, Gennari and Cesari (1965) suggested that the hypercalciuria was primarily absorptive in origin. Peacock, Hodgkinson and Nordin (1967) showed the importance of dietary calcium in demonstrating hypercalciuria, suggesting that the hypercalciuria in stone formers was probably due to excessive absorption of calcium. An implication of this was that idiopathic stone formers were largely drawn from that segment of the population in which absorption and therefore urinary excretion of calcium was above average.

This paper is concerned with the study of a group of stone formers and recurrent stone formers in the Royal Navy in whom intestinal calcium absorption has been measured by arm counting using calcium-47 ( $^{47}\text{Ca}$ ).

In the past, techniques for assessing calcium absorption have required the patient to be in hospital and on a strict metabolic regime and have also required accuracy in the timing and collection of urine, faecal and blood samples. With the availability of  $^{47}\text{Ca}$ , a gamma-emitting radio-nuclide with a half-life of 4.53 days, a relatively simple and accurate method of measuring calcium absorption has become available using external scintillation counting (Curtis, Fellows and Rich, 1967; Wills *et al.*, 1970; Macleod, 1971).

### Methods

All the cases of urolithiasis studied were registered in the Royal Naval Renal Stone Survey, which is supported by grant from the Medical Research Council, and all had a full general and metabolic investigation and excretion urography performed.

The serum calcium, inorganic phosphate, protein and alkaline phosphatase were estimated on at least 4 separate occasions with the patient in the fasting state. Serum calcium was measured by auto-analyser using Technicon Method N3b and the upper limit of normal for this laboratory was taken as 10.5 mg/100 ml.

Urinary calcium excretion was measured first of all with the patient on a diet containing calcium supplements since it has been established that hypercalciuria is only detectable at moderately high calcium intakes (Knapp, 1947; Peacock, Hodgkinson and Nordin, 1967). Thereafter a low calcium diet (150 mg calcium per day) was given and, after a period of 3 days, further measurements of calcium excretion were made to establish the response to this. Urinary calcium was estimated by atomic absorption spectroscopy using the Unicam SP 90.

Gastro-intestinal absorption of radioactive calcium was measured by an arm-counting technique following separate intravenous and oral doses of  $^{47}\text{Ca}$  chloride (Macleod, 1971). This method is

based on the assumption that the distribution in the body of the absorbed part of an oral dose of calcium is identical to that of an entire intravenous dose; thus the fraction of a known intravenous dose, measured in the forearm in this case, will be the same as that of the absorbed dose. Since it has been reported that restriction of calcium intake, as in a low calcium diet, will increase the avidity of the absorptive processes for calcium (Malm, 1958; Heaney and Skillman, 1964; Lloyd, 1967) both a control group and the patients prior to January 1972 were on a normal diet except for a fast of 12 hours before receiving the oral dose of  $^{47}\text{Ca}$  on the 2nd day of the test. For various

**Table I**  
 $^{47}\text{Ca}$  Absorption in Controls

Subject	Percentage Calcium Absorption		
	March 1970	January 1971	July 1972
R. M.	32	...	...
I. L.	30	29	36
H. G.	28	...	...
D. M.	30	...	...
R. L.	26	30	...
P. C.	28	...	...
R. C.	...	26	...
D. S.	29	...	36
P. B.	25	27	26
P. G.	31	...	29
B. G.	...	35	...
D. J.	...	...	36
S. D.	...	...	36
H. P.	...	...	36
N. S.	...	...	35
P. L.	...	...	35
J. S.	...	...	26
A. K.	...	...	25
G. T.	...	...	27
P. C.	...	...	33

reasons during 1972, 49 of 83 patients so tested had started a low calcium diet of 150 mg of calcium per day at the time of the investigation. Of these, the great majority had calcium absorption measured within a day or two of starting the low calcium diet and in no case was the measurement made with the patient more than 5 days on this diet. Comparing the 2 groups, the results showed no statistical difference; 63% of patients on the low calcium diet and 60% of the patients on a normal diet were absorbing calcium excessively. This suggests that a low calcium diet for a short period of time does not influence the process of absorption from the gut. This finding agrees with the observation of Wills *et al.* (1970).

Since the publication of the paper describing this technique (Macleod, 1971) the original 10 control subjects have been augmented by an additional 10 and measurements have been repeated on the previous controls over a period of 3 years. Results in these showed that the amount of the oral calcium dose absorbed from the intestine was between 25% and 36% with a mean of 30% (see Table I).

## Results

125 cases of urolithiasis were studied. Only 2 of this number were female.

Of the 125 patients, 23 (18%) absorbed calcium within the normal range; 102 (82%) absorbed it excessively. The extent of this hyperabsorption of calcium was variable and is shown graphically in Figure 1. Estimations were repeated in a number of these patients over an 18-month period

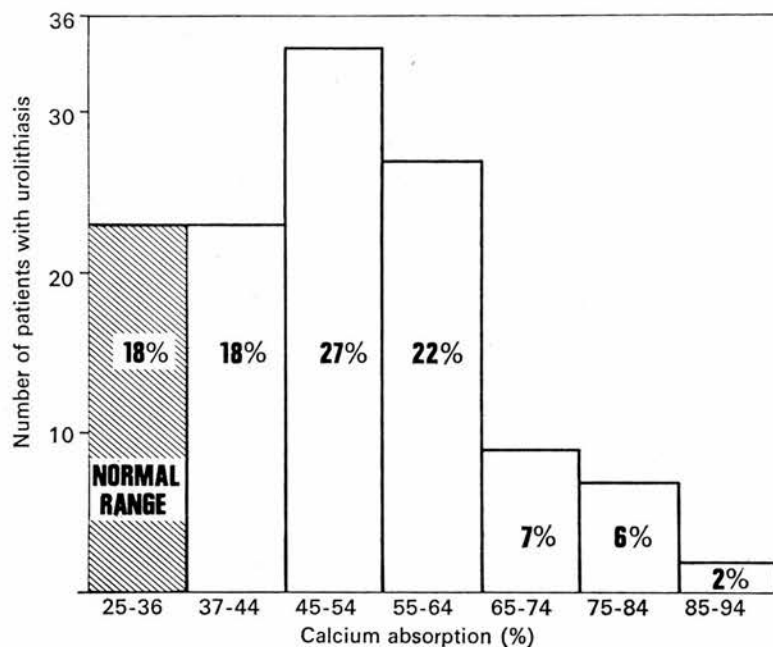


Fig. 1. Variable intestinal hyperabsorption of  $^{47}\text{Ca}$  in 125 cases of urolithiasis.

Table II

Interval Estimations of  $^{47}\text{Ca}$  Absorption in Known Hyperabsorbers

Subject	$^{47}\text{Ca}$ Absorption			
	1		2	
		%		%
T. G. H.	16.11.70	74	13.9.71	60
E. J. H.	16.11.70	64	13.9.71	51
P. J. D.	14.12.70	76	19.6.72	52
B. L. P.	10. 5.71	77	19.7.71	71
H. J. T.	7. 9.70	44	19.7.71	41
J. F.	20. 9.71	76	10.7.72	55

and these showed that the tendency to absorb calcium excessively remained although there was some variation of the extent of this (Table II).

A comparison of calcium absorption with 24-hour urinary calcium excretion in the 125 patients showed that all but 3 who were hypercalciuric were also absorbing calcium excessively from the intestine (Fig. 2). This confirms observations by others (Flocks, 1939; Zisman, Pak and Bartter, 1967; Wills *et al.* 1970).

Two subgroups were formed from the series for comparison. The first was of patients who had formed only a single stone at the time of investigation. The second group comprised those who had formed 2 or more stones in clearly separated instances and were therefore recurrent stone formers. The first group may represent the type of patient in whom stone formation is an isolated

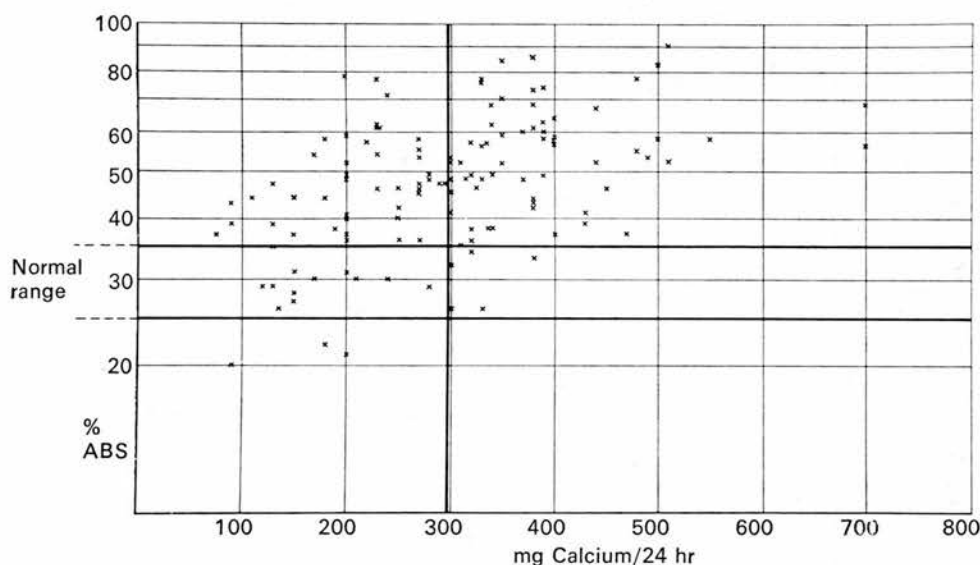


Fig. 2. Comparison of  $^{47}\text{Ca}$  absorption with 24-hour urinary calcium excretion in 125 cases of urolithiasis.

		$^{47}\text{Ca}$ Absorption > 36%	Urinary $\text{Ca}^{++}$ Excretion > 300 mg/day
Solitary stone	78	59 (76%)	31 (40%)
Recurrent stone	47	42 (89%)	36 (77%)

Fig. 3. Comparative incidence of increased  $^{47}\text{Ca}$  absorption and hypercalciuria in solitary and recurrent stone cases.

incident but it is recognised that with a sufficiently long follow-up period some of these could have recurrences at a later date. In other respects both groups appeared to be well matched; the mean age of the single stone formers was 31 years and that of the recurrent stone formers 34. The difference in mean age was not significant.

Of 78 cases of apparently solitary stone, 59 (76%) showed excessive intestinal calcium absorption and 31 (40% of the total) were hypercalciuric. Of 47 cases of recurrent urolithiasis, 42 (89%) absorbed calcium excessively from the intestine and 36 (77% of the total) excreted calcium excessively in the urine at the time of investigation (Fig. 3).



In the single stone formers the mean calcium absorption was 46% (S.D. 13) and the mean 24-hour urinary calcium excretion was 276 mg (S.D. 116). In the recurrent group, mean absorption

	Mean $^{47}\text{Ca}$ absorption	Mean urinary $\text{Ca}^{++}$ excretion
Solitary stone	46% (S.D. 13)	276 mg/day (S.D. 116)
Recurrent stone	56% (S.D. 16)	346 mg/day (S.D. 104)

$P < 0.025$

Fig. 4. Comparison of mean  $^{47}\text{Ca}$  absorption and urinary calcium excretion in solitary and recurrent stone cases.

was 56 (S.D. 16) and mean excretion 346 mg (S.D. 104). The comparison between the 2 groups shows a significant difference ( $\chi^2$  test to one degree of freedom,  $P < 0.025$ ) even with the probability of "contamination" of the first group with a number of potential recurrent stone formers (Fig. 4).

## Discussion

Hypercalciuria has been found to occur in approximately one-third of cases of calcium-containing renal stone in a previous review of cases of urolithiasis in the Navy. The incidence in the present series is 54% but this is a spuriously high figure since the recurrent stone former will tend to be referred to this hospital for full investigation more often than the patient with a single, short-lived incident. Excessive urinary calcium excretion has been ascribed to excessive intestinal calcium absorption (Pyrah, 1958; Harrison, 1959; Parfitt *et al.*, 1964; Peacock *et al.*, 1967). The results from the  $^{47}\text{Ca}$  absorption studies support this concept. They show that a majority of stone formers, whether they are hypercalciuric or not, absorb calcium excessively from the intestine and this is more prevalent in cases of recurrent urolithiasis.

There is only partial correlation between excessive intestinal absorption of calcium and the occurrence of hypercalciuria. All but 3 of the hypercalciurics were found to absorb calcium excessively but 49 patients who were absorbing calcium in excess from the intestine were excreting calcium in normal amounts in the urine at the time of test. Since the  $^{47}\text{Ca}$  absorption test deals only with the percentage absorption of a calcium load it is possible that the normal excretion resulted from a low calcium intake. All patients, however, were on a standard ward diet with calcium supplement in the form of a pint of milk per day besides that taken with cereal, tea and coffee. In the circumstances, if there was a simple linear relationship between calcium uptake and excretion, greater correlation might have been anticipated. However, since hypercalciuria is assessed on the amount of calcium in a 24-hour collection of urine, diurnal variations of calcium concentration will not be apparent; thus, hypercalciuria of varying degree may occur on a number of occasions within a 24-hour period without there being necessarily overall hypercalciuria (Marshall, 1972). It may therefore be inadequate to define hypercalciuria as the excretion of more than 300 mg of calcium in 24 hours in the male and 250 mg in the female (Hodgkinson and Pyrah, 1958). Rose (1967) has pointed out that the normal range of urinary calcium varies from one country to another and may also vary within a country since Watson and Dale (1966) consider that in London the excretion of up to 400 mg of calcium per day is normal for a man and 300 mg per day for a woman.

In this series, however, there appears to be closer correlation between the intestinal calcium uptake and urinary calcium excretion in the recurrent than in the apparently solitary stone formers.

An implication of the finding of an increased absorption of calcium in a high proportion of cases of urolithiasis is that greater quantities of calcium are being presented to the excretory system and the nephron in particular for excretion. With its known toxicity when present in excess, cellular damage due to high local concentrations of calcium might occur in the cells of the nephron or its interstitial tissues. This may be an interpretation of the finding by Anderson (1968) of foci of calcium phosphate precipitation in the kidneys of patients with a history of renal stone. Similar foci were present in patients who had no history of stone formation but were significantly more prevalent in the stone-forming group in which they occurred in 64%. Malek and Boyce (1973) describe calcium deposits in the kidneys of all of 52 cases of idiopathic calcium oxalate stone. These observations bear comparison with the present finding of excessive intestinal absorption of calcium in 82% of this group of stone formers.

In Anderson's series the calcium phosphate was present within the interstitial tissues and the epithelial cells of the renal tubules, sometimes extending into the lumen; the loop of Henle and the collecting tubules were most frequently involved. Boyce (1972) in a study of biopsies of human kidney found Periodic Acid Schiff (PAS) positive material, usually with concentric laminar structure and containing calcium in significant quantities, within the lumen of the nephron. He considered that the origin of this material was in the proximal renal tubule and that there was subsequent migration to the collecting ducts. He attributed the high incidence of medullary concretions to the coalescing ductal anatomy. Cooke (1972) in a radio-isotope study demonstrated a marked calcium concentration gradient ranging from maximal in the papilla tip to minimal in the cortex of the kidney; he also found differences in the calcium content of anatomically comparable regions of the kidney when he compared specimens from a population group with and another without a tendency to form renal stones.

It is well known that calcium salts tend to be deposited in tissues which are already damaged or undergoing degeneration. Scarparelli, Tremblay and Pearse (1960), in drawing attention to this, pointed out that the damaging agent in some cases could be an excess of calcium itself. Cells which are involved in the metabolism or transport of calcium—as are the cells of the nephron—are probably protected against its toxic effects within certain limits. An excess of calcium, however, may overwhelm a protective mechanism and result in tissue damage and subsequent calcium deposition.

The lesions described by Anderson (1968) and others may therefore be primary and stone formation in the tubules and calyces a secondary phenomenon due to crystallisation on a calcified nidus extruded from the epithelium of the tubules. They may be a direct consequence of a metabolic abnormality resulting in the increased intestinal absorption of calcium as found in such a high proportion of this series of stone formers.

### Summary

The intestinal calcium absorption was measured in a group of stone formers using an external isotope counting technique.

Hyperabsorption was found in 82% and was even more prevalent in the recurrent cases.

Comparison of absorption with urinary calcium excretion showed greater correlation in a group of recurrent stone formers than in cases of apparently solitary stone formation.

The finding of intestinal hyperabsorption of calcium in a high proportion of stone formers may be aetiologically significant in the parenchymal calcium deposition found in these cases.

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# The Effect of Cellulose Phosphate on Intestinal Absorption and Urinary Excretion of Calcium

## Some Experience in its use in the Treatment of Calcium Stone Formation

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The findings in a previous paper have provided further support for regimes of treatment which reduce the intestinal uptake of calcium and therefore its urinary excretion in the management of recurrent calcium urolithiasis (Blacklock and Macleod, 1974).

Dietary measures have already been used towards this end and Nordin (1972) considers that a diet low in calcium and low in oxalates is the simplest and most effective approach in the treatment of this condition. Sodium phytate has been shown to form a relatively insoluble complex with calcium in the gut and the effect of this has been to lower urinary calcium in patients with idiopathic hypercalciuria (Henneman *et al.*, 1958); there is however an increase in urinary phosphate excretion at the same time (Parfitt *et al.*, 1964). Oral administration of sodium phosphate similarly has the effect of reducing intestinal calcium absorption and urinary calcium excretion but the urinary phosphorus excretion in the form of orthophosphate increases at the same time. Therapeutic use of both sodium phytate and sodium phosphate is therefore accompanied by a possibility of increased tendency to calcium phosphate precipitation on account of the increase in its activity product ratio. (Pak *et al.*, 1971). The thiazides as a group reduce urinary calcium excretion and increase renal excretion of phosphate as pyrophosphate with a concomitant increase in the urinary sodium and potassium. Calcium balance studies carried out at the time of thiazide treatment suggest that calcium is retained during such treatment (Lamberg and Kuhlback, 1959; Lichwitz *et al.*, 1961; Higgins *et al.*, 1964; Yendt, Gagne and Cohamin, 1966; Harrison and Rose, 1968).

Sodium cellulose phosphate, the sodium salt of the phosphoric ester of cellulose (Whatman Biochemicals Ltd) is an ion exchange cellulose with special affinity for divalent cations because of the steric configuration of the phosphate radicals attached to the cellulose molecule. In the stomach it exchanges sodium for calcium which is eliminated in the faeces so preventing the absorption of dietary calcium; it similarly binds with secreted calcium preventing its reabsorption. The diminution in calcium absorption is accompanied by a reduction in the renal excretion of calcium and a slight increase in urinary phosphorus but the urine saturation with brushite ( $\text{CaHPO}_4 \cdot 2\text{H}_2\text{O}$ ), a probable nidus for calcium stones, is reduced (Pak, 1973).

This paper describes some observations on the effect of sodium cellulose phosphate on intestinal calcium uptake and urinary calcium excretion in patients with urolithiasis. Further observations are made on the results of a limited clinical application of the substance.

## Materials and Methods

### Clinical Data

The effect of cellulose phosphate was evaluated in a series of patients who exhibited intestinal hyperabsorption of calcium and hypercalciuria. All had full general and metabolic investigation including excretion urography. Cases of overt hyperparathyroidism were excluded.

### Analytical Procedures

Intestinal calcium absorption was assessed by the technique of external radioisotope counting described in a previous paper (Macleod, 1971). The normal range of absorption established by this method was 25% to 35% of the calcium meal.

Urinary calcium excretion was measured with 24-hour specimens of urine by atomic absorption spectroscopy using the Unicam SP 90. Hypercalciuria was taken as the excretion of more than 300 mg of calcium per day in the male and more than 250 mg calcium per day in the female (Hodgkinson and Pyrah, 1958).

The serum calcium, inorganic phosphate, protein and alkaline phosphatase were estimated on at least 4 separate occasions at the outset and at each attendance for follow-up examination with the patient in the fasting state. Serum calcium was measured by auto-analyser using Technicon Method N3b and the upper limit of normal for this laboratory was taken as 10.5 mg/100 ml. Serum iron, copper and magnesium were measured at the outset in each patient and at each follow-up examination subsequently. Serum iron was measured by Richterich's method and copper and magnesium by atomic absorption spectroscopy (Unicam SP 90).

### Results

Initially the effect of sodium cellulose phosphate on  $^{47}\text{Ca}$  uptake was evaluated in various conditions of dosage and administration. In the tests described in paragraphs 1 and 2 below the sodium cellulose phosphate was taken in water within 5 minutes of an oral dose of  $^{47}\text{Ca}$  chloride on the second day of an absorption test.

#### Laboratory Findings

1. In 10 patients who were given 5 g of the substance there was a marked reduction in  $^{47}\text{Ca}$  absorption (Table I).

**Table I**

Effect of Cellulose Phosphate on  $^{47}\text{Ca}$  Absorption in Cases Known to Absorb Calcium Excessively from the Intestine

Subject	$^{47}\text{Ca}$ Absorption	
	Before CP	After CP
	%	%
K. D.	70	11
T. G. H.	60	19
R. B.	58	16
E. M. F.	76	23
B. B.	67	16
T. P.	84	26
A. M.	57	18
P. G.	77	15
C. E. B.	77	18
N. J. F.	91	32

2. The dose of the substance was varied. Two cases each received 1 and 2 g respectively and a fifth was given 3 g and then 5 g in an uptake test (Fig. 1). The effect appeared to be dose related. Five grams reduced the intestinal calcium by as much as 85% and even a 1 g dose resulted in a 50% reduction. The 5 g sachet provided as the standard dose therefore has a wide margin for effective action in this respect. Such a dose, however, is probably essential when it is considered that the substance will ordinarily be dispersed throughout a semi-solid food bolus.

Urinary calcium excretion was measured concurrently with the various dosages of sodium cellulose phosphate and appeared to be reduced commensurately with the dose (Fig. 2).

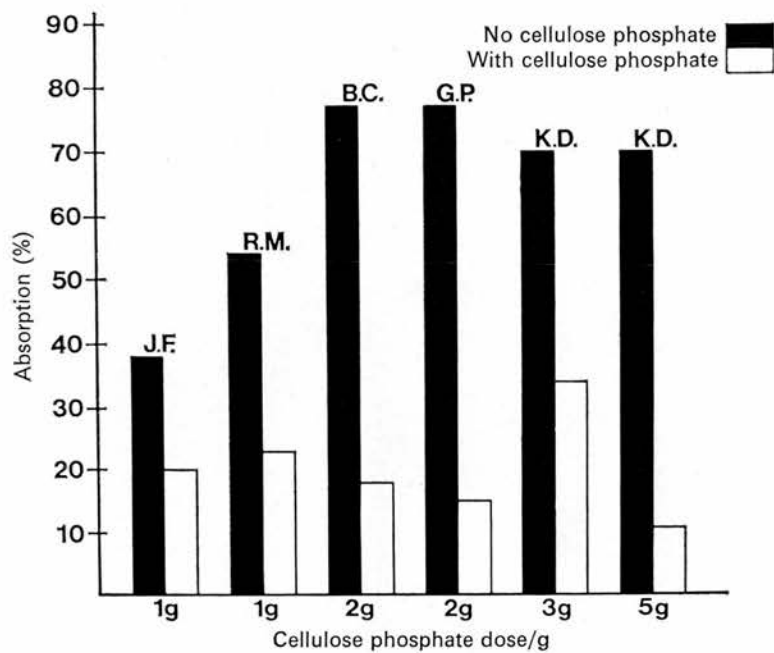


Fig. 1. Effect of variable dosage of sodium cellulose phosphate on intestinal calcium absorption.

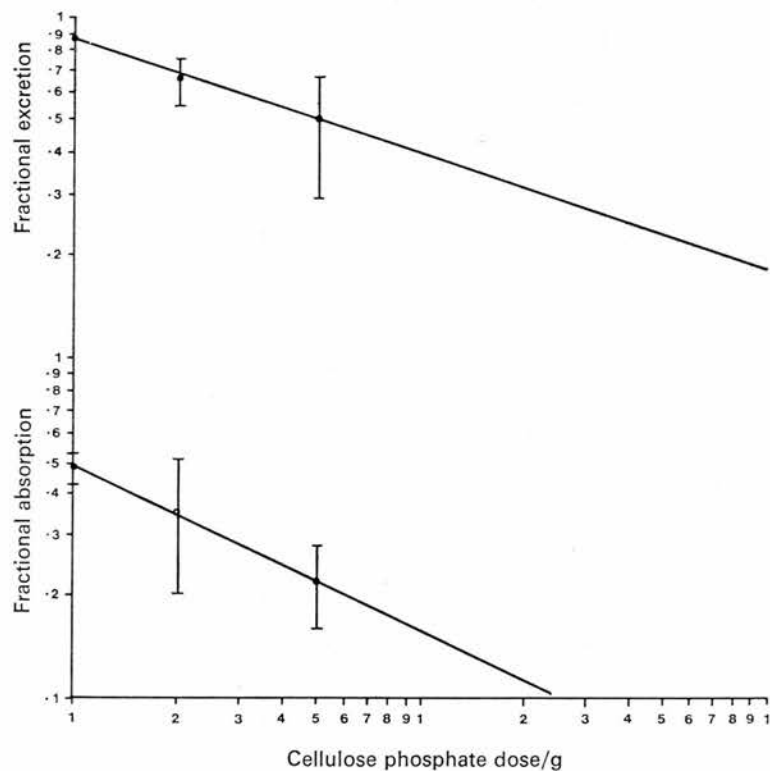


Fig. 2. Comparison of the influence of varying dosage of sodium cellulose phosphate on intestinal absorption and urinary excretion of calcium.



3. The influence on calcium absorption of taking a 5 g dose of sodium cellulose phosphate at variable intervals of time from a calcium meal was evaluated (Fig. 3).

Maximum effect was achieved if the substance was taken with a meal or within 1 hour thereafter. There was a marked reduction in effect if the substance was taken more than 1 hour afterwards. Bearing in mind that the calcium meal was in liquid form in these tests, it is likely that the dose relationship of sodium cellulose phosphate to a normal meal is even more critical.

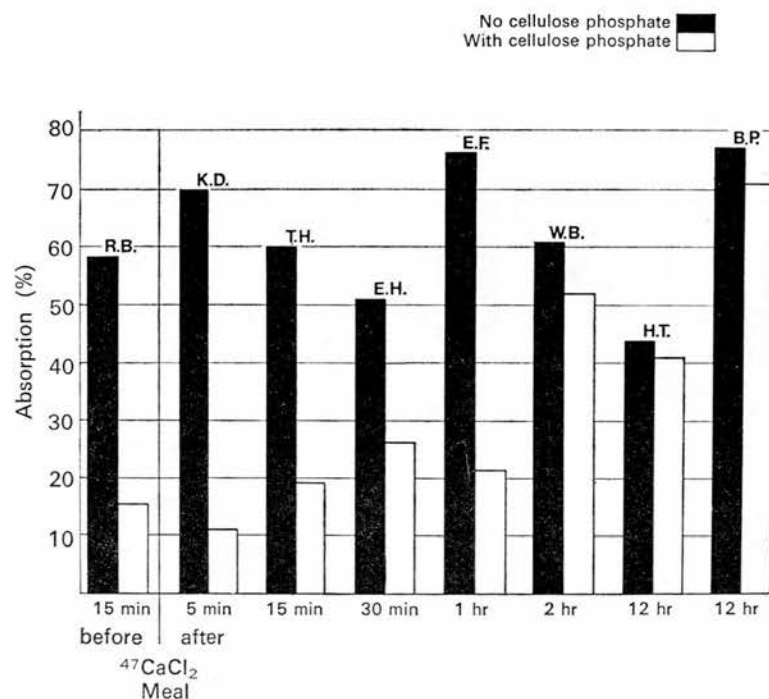


Fig. 3. The influence of time between a calcium containing meal and dose of sodium cellulose phosphate on the reduction of intestinal calcium absorption.

4. The effect of the substance on urinary calcium excretion was assessed in a number of patients with hypercalciuria of varying degree (Fig. 4). In all of these, 5 g of sodium cellulose phosphate taken 3 times daily at the time of meals, effectively reduced urinary calcium excretion to within normal levels.

5. *Other observed effects of sodium cellulose phosphate administration.* Serum levels of calcium and phosphorus were not altered in any of the patients even when the substance had been taken for a period as long as 7 years in a dose of 5 g 3 times daily.

Since the action of sodium cellulose phosphate is not selective as regards the divalent cations it can absorb, there is the theoretical possibility of trace metal deficiencies in long-term usage. Dent, Harper and Parfitt (1964) found a fall of plasma magnesium from 2.0 to 1.4 mEq/l. Pak (1973) noted a reduction in the serum concentration of magnesium and its renal excretion in a majority of cases. He found that it did not significantly affect the metabolism of copper or zinc. Pietrek and Kokot (1973) noted a trend towards reduction in the levels of serum magnesium, iron, copper and zinc concentrations although this was not statistically significant.

In the present series of cases who were treated without magnesium supplement for various periods of time there appears to have been little significant effect on plasma magnesium. One



case treated for more than 4 years has a serum magnesium of 2.2 mg %; another treated for a similar period, however, has a level of 1.4 mg %.

Serum copper and iron appear to have been largely uninfluenced although no statistical evaluation of these results has been carried out. In 2 cases who have had the substance for more than 3 years the serum iron at present is 50 and 60  $\mu\text{g}$  per 100 ml respectively, the lower level of normal (Fig. 5).

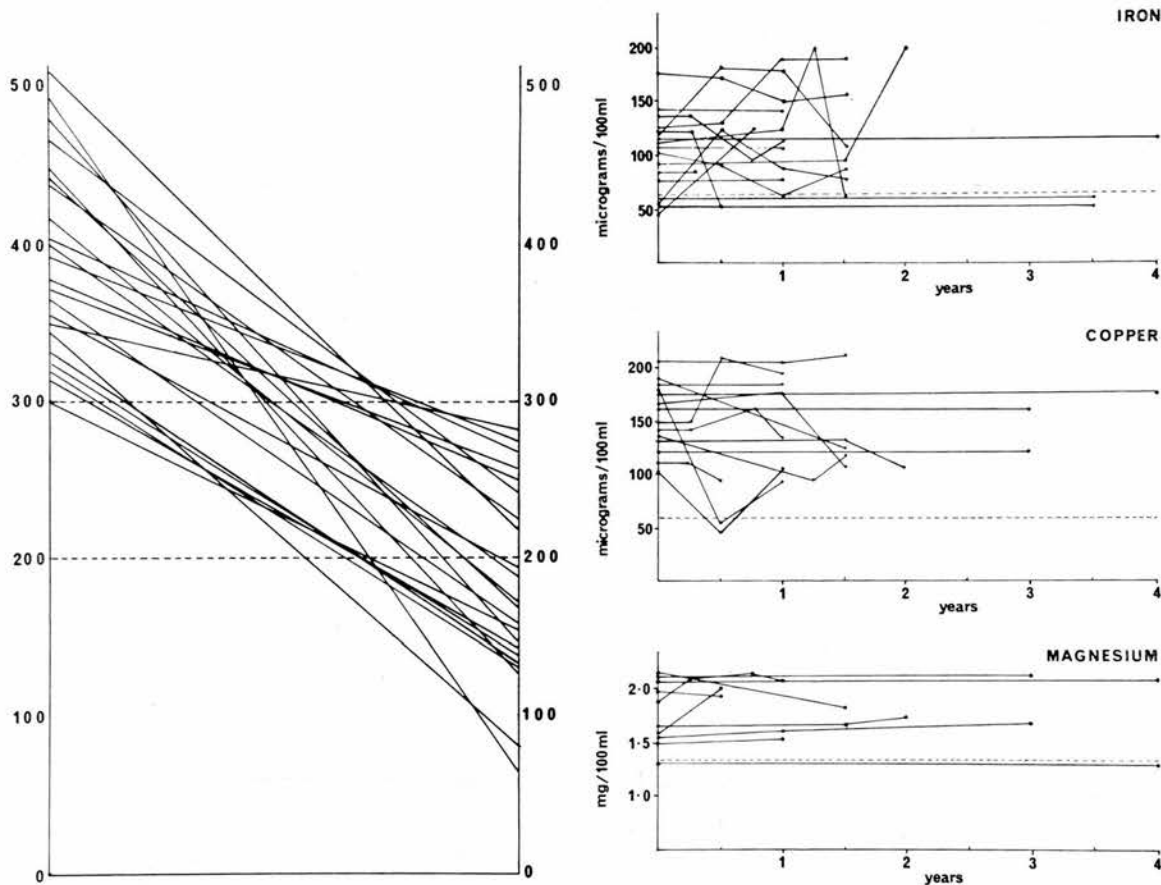


Fig. 4

Fig. 5

Fig. 4. Effect of sodium cellulose phosphate on urinary calcium excretion in 22 cases of idiopathic hypercalciuria and stone formation.

Fig. 5. Variation in serum levels of iron, copper and magnesium with long-term sodium cellulose phosphate treatment.

#### *Clinical Experience with Sodium Cellulose Phosphate in Recurrent Calcium Urolithiasis*

All cases treated with sodium cellulose phosphate had a history of recurrent urolithiasis and were hypercalciuric. The duration of treatment up to the present time is variable, ranging from some months to several years.

Sodium cellulose phosphate is easy to take and is quite palatable. Intestinal upset and diarrhoea which had been noted by others (Harrison *et al.*, 1972) have not been encountered.

The urinary calcium excretion has been measured in a number of patients at various intervals of time from the commencement of treatment. In 2, hypercalciuria persisted but a subsequent satisfactory reduction in calcium excretion has followed supplementing the treatment with a low

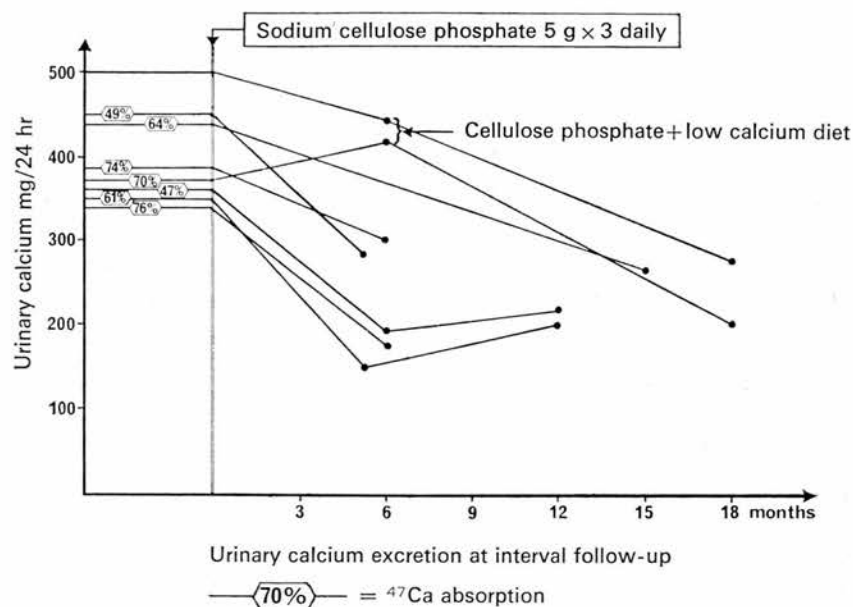


Fig. 6. Urinary calcium excretion at various intervals from commencement of treatment with sodium cellulose phosphate.

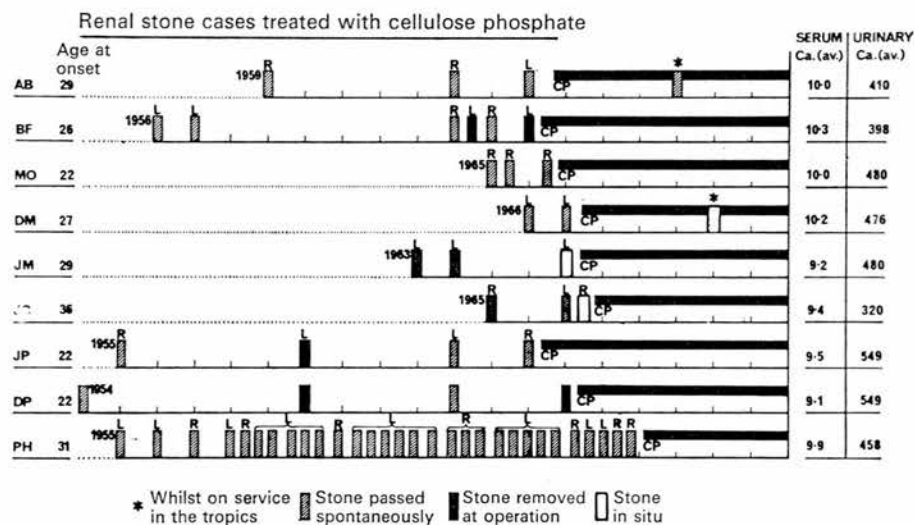


Fig. 7. Graphic representation of stone incidents in 9 cases both before and after the commencement of sodium cellulose phosphate treatment.

calcium diet. One of these cases had a  $^{47}\text{Ca}$  uptake of 70%. The majority show a satisfactory reduction of calcium excretion to within normal rates (Fig. 6).

Pietrek and Kokot (1973) have found the urinary calcium to be maintained consistently at reduced levels but others (Rose and Harrison, 1972) have had the impression that the initial reduction is not maintained after a time. This is probably a measure of the tendency to default with treatment rather than an indication of the development of resistance in some form to its effect.

Both Pak (1973) and Pietrek and Kokot (1973) already have some evidence of a reduced frequency of stone incidence with this treatment. The effect of the preparation in a number of patients in this series who have been treated for several years is shown graphically (Fig. 7).

Only 2 new stones have been formed in the 9 cases depicted; in both of these there was an additional aggravating factor of service in a tropical climate at the time of the recurrence and both were engaged on watchkeeping duties at sea when there was difficulty in relating cellulose phosphate dosage to irregular meals. Case P. H. has shown the most significant response; this patient had consistently formed several stones annually from 1955 until the time of starting treatment with sodium cellulose phosphate in 1969; the majority of stones passed had been calcium oxalate but several were "mixed"; since the commencement of treatment there has been no further instance of urinary colic or passage of a stone and his urinary tract is demonstrably clear of opaque calculi at the present time, *i.e.* 1973. No other therapy or dietary means of control has been adopted by this patient in the meantime. No statistical evaluation of this series has been attempted at this time.

## Discussion

Previous work (Blacklock and Macleod, 1974) has shown excessive intestinal absorption of calcium in a significantly high proportion of calcium stone formers. In a group of apparently solitary stone formers 76% absorbed calcium excessively. In a series of recurrent stone formers, 89% showed excessive calcium absorption. Hypercalciuria occurred in 40% of those with an apparently solitary stone and in 77% of those who had formed more than one calcium stone. These findings provide further support for a rationale of treatment directed at reducing intestinal calcium absorption and, through this, the renal filtered load of calcium and the urinary calcium excretion.

This may be effected in whole or in part by dietary control and Nordin (1972) has described a low calcium, low oxalate diet as the simplest and most effective regime. Dietary control, however, whilst being an ideal form of management in a metabolic unit poses formidable day to day difficulty to a patient and these difficulties are compounded when circumstances necessitate meals away from home as when travelling and when feeding is institutional. In these circumstances there is the need for an effective agent to reduce the absorption of ingested calcium. Sodium cellulose phosphate is demonstrably effective in this respect and so far has proved innocuous. It is considered that there is a case for its use, suitably monitored, in cases of recurrent urolithiasis who have been shown to absorb calcium excessively from the intestine and to be hypercalciuric.

## Summary

Sodium cellulose phosphate can significantly diminish the absorption of calcium from the intestine; there is concomitant diminution of urinary calcium excretion. The plasma levels of the divalent cations do not appear to be influenced by this therapy.

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